THE EPIDEMIOLOGY OF HODGKIN'S DISEASE IN NEWFOUNDLAND

SHARON LYN KELLY BUEHLER

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by

©Sharon Lyn Kelly Buehler

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ABSTRACT

From 1954 to 1973, seven cases of Hodgkin's disease occurred in a population of 1500 people on the west coast of Newfoundland. In contrast, published figures indicated that incidence was low in the province as a whole. This regionally high frequency of cancer within a province where Hodgkin's disease was thought to be uncommon required clarification.

The objectives of this thesis were to verify the low incidence with well documented figures, to critically evaluate the data sources, and to suggest possible reasons for the infrequent occurrence of this cancer in Newfoundland.

There were four sources of data; death certificates, hospital records, radiation oncology records, and records from the cancer registry were used to collect information on every case of Hodgkin's disease recorded in Newfoundland from 1965 to 1974.

The main findings were 1) Hodgkin's disease incidence in Newfoundland from 1965-74 was low; 2) typical of the Type II pattern of Hodgkin's disease, this low incidence was associated with a relatively large number of cases in young males and with histological types with poorer prognosis; 3) patients were more likely to have worked in professional and skilled occupations and 4) were more

likely to have been born in late summer; and 5) Canadian incidence was associated with standard of living while crowding appeared to be a better predictor of Newfoundland incidence. No one data set was sufficient to locate all cases or to provide all information needed. Of the errors and omissions in data sources, the most serious was the large discrepancy in the medical insurance number and the date of birth which it incorporates.

The frequency of patient births in late summer raises the possibility of an environmental agent working at the time of conception or at birth.

If incidence is due in part to socioeconomic factors, then the improvement in standard of living should eventually modify incidence upwards. Therefore it is suggested that Hodgkin's disease in Newfoundland is in transition to a Type III pattern providing a unique opportunity to document the environmental factors associated with this change.

DEDICATION

To Dick, Kelly, and Michael

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDIX TABLES AND FIGURES

SECTION 1. INTRODUCTION

A. BACKGROUND TO THE PROJECT

In the spring of 1973, a thirty-year old man from the west coast of Newfoundland was admitted to the General Hospital, St. John's, for investigation of recurring respiratory infections. He was found to have common variable immunodeficiency (acquired immunodeficiency or A.I.D.); both cell-mediated and humoral immunity were depressed (Marshall et al., 1980). During discussion of his case, it was learned that a number of patients from that region of the province had been treated for lymphoma.

Preliminary field work revealed that eleven cases of lymphoreticular malignancy, seven of them Hodgkin's disease, had been diagnosed in that area since 1954. All of the cases were part of a kinship comprising the majority of the residents of three small communities. All could be traced back to a single founder couple who arrived on the west coast in approximately 1830 (Buehler et al., 1975). An abridged version of the pedigree is given in Figure 1 and Table 1 of the Appendix, pp. A-1-2.

Further investigation found four other cases of lymphoma, one of them Hodgkin's disease, and two more immunodeficiencies. Again, all were part of the large kindred. Averaged over the 10 year period in which six of

the seven Hodgkin's patients were diagnosed, and including the three non-familial patients in this area, the incidence in that census division was twice that of the whole province. The three communities involved had only six percent of the population of the division in 1971.

Discussion of the preliminary findings in a multidisciplinary seminar led to the establishment of field clinics on the west coast of Newfoundland in the summer of 1974 with followup clinics in 1975 and 1976 (Marshall et al, 1975). From the beginning of this collaborative project it was accepted that this aggregation of lymphoreticular malignancies should be put into perspective against baseline data for the whole province. In published incidence and death data (see Section IV, p. 153), the rates of Hodgkin's disease in Newfoundland had been consistently lower than in Canada as a whole. The question of whether these rates were truly low or could be attributed to problems with case ascertainment was the starting point of this thesis.

B. OVERVIEW OF HODGKIN'S DISEASE

An overview of Hodgkin's disease is presented here; a detailed review of the literature with complete references is given in Section III, p. 14. One hundred and fifty years ago, in 1832, Thomas Hodgkin's paper on "Some Morbid Appearances of the Absorbent Glands and Spleen" was

read at the January meeting of the Medical-Chirurgical Society in London, England. It described seven cases of what has come to be known as Hodgkin's disease. Other clinicians and anatomists had, no doubt, observed the condition. David Craigie had described such a disorder in 1828 in a text on pathological anatomy and referred to an earlier case report by Cruickshank in 1786. But Hodgkin was the first to suggest as a distinct disease the peculiar condition of the lymph glands which resembled inflammation but behaved as a malignant growth. Nearly a quarter of a century later, in 1865, Sir Samuel Wilks described four of Hodgkin's cases. Wilks had considered his own observations original but on hearing of the earlier work, searched out Hodgkin's paper and appended his own article with a comment on the condition he termed "Hodgkin's disease".

Hodgkin's disease is a condition involving the lymphatic system. Presenting symptoms vary. There may be swollen lymph nodes and fever, pruritis, night sweats, lethargy, and, occasionally, weight loss. There may be no symptoms; a number of cases are picked up accidentally through routine physical examinations at work or school. A previously undetected lump may be found or a mediastinal mass is seen on a routine x-ray. Because the symptoms are often vague and are shared with a number of other diseases, biopsy is the only certain method of diagnosis.

The pathology is varied; four histological subtypes are currently recognized. The classification of Hodgkin's has developed over the last four decades and is still under active discussion. Advances in assessing the extent of disease have improved treatment. Survival has increased dramatically.

The presence of the Sternberg-Reed cell in the biopsy specimen is necessary for the diagnosis of Hodgkin's disease. This large multinucleate cell with prominent nucleoli which give it an owl-like appearance, was described by Sternberg in 1898 and Reed in 1902. It is also found in the lymph nodes of patients with infectious mononucleosis and, occasionally, in other conditions. Early changes in Hodgkin's disease are, therefore, sometimes difficult to distinguish from these conditions and from chronic inflammatory reactions which produce similar signs.

The age incidence curve which peaks bimodally in the young adult and in the elderly is a peculiarity of Hodgkin's disease. It was first described by MacMahon in 1957 (see Figure 2 of the Appendix, p. A-3) and has led to speculation that Hodgkin's is really two diseases, an inflammatory disorder in the young and a malignant process in the elderly.

Although aggregations of Hodgkin's disease patients had been reported previously in the literature, it was a

series of articles by Vianna and his group on a cluster of young Hodgkin's patients in New York state that led to serious consideration of the possible horizontal transmission of the disease. The majority of Vianna's cases were students who had been in the same high school class or in close contact with a member of that class. The possibility of an infectious agent gained strength as reports of investigations of African Burkitt's lymphoma and infectious mononucleosis described the association of these two diseases with the Epstein-Barr virus.

Reports of more than one case of Hodgkin's disease in a family are uncommon but not rare. There are many reports in the literature of multiple cases of Hodgkin's disease and lymphoma in families; the west coast study is one of these (see Section IIIB, p. 28). Razis in 1951 and, a short while later, Devore and Doan reviewed reports of familial cases and found a threefold increase in risk in first degree relatives of Hodgkin's patients. More recently Grufferman has shown this risk to be increased in siblings, particularly of the same sex. In most studies, the dates of onset correspond more closely than the ages at onset. This is a finding expected in a disease with an environmental etiology.

Finally, Hodgkin's disease has an intriguing geographic distribution. More severe forms of the disease are seen in children in poor regions of the world and more

benign forms are found in young adults in industrialized countries. Poliomyelitis in the pre-vaccine era showed a similar pattern; young children in poorer populations were affected with severe and often fatal disease. And, in more prosperous countries where a higher standard of living discouraged early infection with the virus, persons were susceptible to the disease at older ages.

Detailed description of these aspects of the disease and of other variables associated with higher risk of Hodgkin's disease will be found in the literature review, Section III, p. 14.

C. OVERVIEW OF NEWFOUNDLAND

More complete accounts of Newfoundland's history, demography, culture, and economy may be found in Statistics Canada census publications and in the publications of the Institute of Social and Economic Research (ISER), Memorial University. Newfoundland is the oldest colony of Britain and the youngest province of Canada. It was discovered by John Cabot in 1497 and its rich fishing banks have drawn fleets from all over the world. The colony's administration changed back and forth between the French and the English several times until 1825 when the first English civil governor was appointed. Permanent settlers were predominantly from the southeastern counties of

Ireland and from the West Country of England. The Scots and the French settled along the west coast of the island. These groups in their isolated settlements preserved many of their homelands' traditions so that today dialects, songs, stories, and customs long lost in their countries of origin are retained here. Indian and Innuit inhabit Labrador and Indians live in several small areas of the island. Although they have, to some extent, intermarried with white settlers, they are regarded as separate cultural groups.

Newfoundland, including the huge land mass of Labrador and the smaller island, comprises 156,185 square miles of forested wilderness dotted with lakes. Settlement, both on the island and in Labrador, began and continues for the most part along the coastline (see Figure 3 of the Appendix, p. A-4). The population in 1981 was 567,681. Fifteen percent of the inhabitants live in the capital city, St. John's, and ten percent in five other major towns. The remainder of the population is scattered in small settlements averaging 500 people. The traditional occupations, fishing and logging, continue as seasonal jobs for many men. Changes in government funding for ship-building, compensation for lost gear, and, particularly, licensing, have made it unprofitable for many small fishermen to continue in the fishery, particularly in a bad year. Except in major cities, the majority of women are homemakers although

an increasing number work seasonally in the fish plants scattered throughout the province and in jobs connected with the tourist industry. More women have also become involved in local politics and development programs.

Attempts at industrialization have been of limited success. Aside from mining ventures and, during the war, military bases, the economy has been mostly dependent on the fishery and woods operations.

Newfoundland has the highest cost of living of Canadian provinces and the next to lowest average income. Unemployment in 1981 was 15.2 percent, the highest in the country.

The gradual connection of settlements by road, although still incomplete, has provided a greater exchange of people and goods. Some areas of the province are still without day-round electricity and others have limited radio and television reception, but generally better communication has meant exposure to many new ways of doing things. As roads improve and refrigerated transport is more widely available, home frozen and canned foods are being supplemented with increasingly available fresh frozen meat, dairy products, and produce. Commercial tinned foods, relatively new dietary items in the 1940s, are now seen in greater variety in the small stores in the coastal settlements or outports.

The large extended family has become decentralized as the younger members leave to attend university and move on to professional occupations or migrate outside their communities or the province to find jobs in the higher paying oil, mining, and pulp and paper industries. With fewer family members in the community and with more women out at work or actively involved in local programs, more of the elderly and handicapped, formerly cared for in the home, must find institutional care. Illegitimate children or love children, previously taken into a grandparent's home, are now occasionally put up for adoption or, more frequently, kept by the single mother. The strong traditions of, particularly, the Anglican and Catholic churches are being replaced in many communities by those of fundamentalist sects or lost altogether in a drifting away from the church. A population once dependent mostly on themselves for routine medical care is now putting greater demands on the cottage hospital system and the thin network of private practices across the province.

The general rise in the standard of living and the influx of mainly skilled and professional people from outside Newfoundland have forced many changes. The disparity between city and outport remains although federal-provincial improvement programs have resulted in better housing, sewage, and water supply, and media coverage

has led, with some success, to local demand for more sophisticated services.

Newfoundland is, therefore, undergoing major changes in lifestyle. These changes will, no doubt, be reflected in disease incidence. Consequently, for diseases thought to be influenced by diet, occupation, the social support system, and, generally, the standard of living, there is unique opportunity in Newfoundland to assess the impact of change on disease. If Hodgkin's disease is more common in persons from small families who have a higher level of education and who work in professional occupations, then one would expect Newfoundland incidence to be low in relation to other areas in North America, at this time. But we would expect incidence to increase. By carefully marking the current status of Hodgkin's disease in the province, we can, in future years, more accurately evaluate the role of various socioeconomic factors in the etiology of this disease.

SECTION II. AIMS OF THE THESIS

Published government statistics have repeatedly shown the incidence of Hodgkin's disease in Newfoundland to be lower than the Canadian average. On the other hand, in one area of the province, an unusual number of cases has been documented in a small population. The work for this thesis is designed to obtain, through a number of sources, accurate incidence figures for the province for a ten year period. A detailed description of the status of Hodgkin's disease based on complete case ascertainment would allow 1) analysis of the data to explain Newfoundland's lower rates 2) comparison of the high incidence area with the rest of the province and 3) evaluation of the information sources.

The work of this thesis has been formalized in the following hypotheses:

1. The incidence of Hodgkin's disease in this province is low.
2. The low incidence can be at least partly explained by socioeconomic factors currently believed to be associated with Hodgkin's disease.
3. The aggregation of cases on the west coast of the island is an unusually high incidence in a province where Hodgkin's disease is a particularly infrequent cancer.

The testing of these hypotheses is approached through standard epidemiological analyses and through evaluation of the data used in those analyses.

A. EPIDEMIOLOGY OF HODGKIN'S DISEASE IN NEWFOUNDLAND

One of the aims of this project is to provide complete baseline data i.e., incidence, prevalence, and mortality, on Hodgkin's disease in Newfoundland. Using the final lists of patients diagnosed, treated, or dying during the period 1965-1974, crude, adjusted, and age-specific incidence and death rates will be calculated for the province. Crude and adjusted rates will be calculated for census divisions. Rates will be compared among census divisions, between Canada and Newfoundland, among provinces, and among selected countries. Prevalence will be calculated for census divisions and for the province.

Secondly, sex ratios, frequencies of clinical stage and histopathological type, and survival rates will also be calculated. The geographic distribution by residence at diagnosis and by residence at birth will be plotted.

Finally, depending on the availability of information, a number of factors found in other studies to be associated with increased risk of Hodgkin's disease will be reviewed for this series.

B. QUALITY OF AVAILABLE DATA

Because of Newfoundland's small population, the centralization of treatment facilities, and the location of the major referral hospital in the capital city, it has been assumed by persons in both clinical and academic medicine, that record reviews in this province would be simpler than in other more populous areas with less centralized health care delivery. One of the objectives of this study will be to test this assumption by determining the accessibility, completeness, and reliability of the data available for Hodgkin's disease. Four data sources will be surveyed: death certificates, hospital records, radiation oncology records, and tumor registry records. The data sources will be reviewed for 1) deficiencies and errors in files, 2) deficiencies and errors in individual records, and 3) methods of storage and retrieval of records.

SECTION III. REVIEW OF THE LITERATURE

A. INTRODUCTION

The study of the aggregation of cases of lymphoreticular malignancy and immunodeficiency on the west coast of Newfoundland permitted the major etiological hypotheses about Hodgkin's disease, i.e., the roles of possible viral transmission and of host susceptibility to be examined. Hodgkin's disease may be viewed as a contagious disease of low pathogenicity contracted by an immunologically compromised host. The defect in immune defense may be temporary or it may put the host at risk throughout his life time or, more likely, for some particularly vulnerable period in his life. The infectious agent is unknown. The postulated infection would be expected to be widespread in the population and involved in a number of clinical and subclinical conditions. In summary, there are likely to be both time and space factors in the pathogenesis of Hodgkin's disease which involve a particularly susceptible host at the right age in the right environment at the right time.

In the review following, the first section will deal briefly with the recognition of Hodgkin's disease, its histopathology, clinical presentation, treatment, and

survival with a short section on the problem of second primaries following treatment.

The second section presents the literature on the occurrence of Hodgkin's disease in families beginning with a summary of the findings to date of the west coast study. This investigation of a large familial cluster of Hodgkin's disease and lymphoreticular malignancy led directly to the work of this thesis.

The final section reviews the literature on the epidemiology of Hodgkin's disease. The early papers are discussed in the introduction followed by a review of the geographic distribution of the disease. Certain risk factors seem to be of primary importance in untangling the etiology of Hodgkin's disease; recent research on these is also presented.

1. History

Since the first description of Hodgkin's disease, there has been much controversy over the nature of this disease. Hodgkin's first report described the autopsy in 1826 of nine year old Joseph Sinnott of Guy's Hospital, London.

> It may be observed that not-withstanding some differences in structure, to be noticed hereafter, all these cases agree in the remarkable enlargement of the absorbent glands accompanying the larger arteries....Notwithstanding the different characters which this enlargement may present, it appears nearly in all cases to

> consist of a pretty uniform texture throughout and this rather to be the consequence of a general increase of every part of the gland, than of a new structure developed within it, and pushing the original structure aside...the new material by which the enlargement is effected, presents various degrees of organizability, which in some instances is extremely slight and appears incompetent to maintain the vitality of the affected gland....Another circumstance which has arrested my attention, in conjunction with this affection of the absorbent glands, is the state of the spleen which, with one exception in all the cases that I have had the opportunity of examining, has been found more or less diseased, and in some thickly pervaded with defined bodies of various sizes, in structure resembling that of the diseased glands (Hodgkin, 1832).

Hodgkin considered the disease a kind of "hypertrophy of the lymphatic system". Wilks later commented that "an interruption to the healthy action of the body is induced by the excessive function of one set of organs", adding that

> It would appear that this disease represents merely one mode in which an adventitious deposit can affect the organs and that it must take its place in the ranks of malignant diseases, or amongst those affections which are characterized by the development of new growths in the system...the lymphatic glands appear to be affected for a considerable period, perhaps many years, before the system suffers, and that next the spleen becomes especially involved, and afterwards, the other organs (Wilks, 1887).

2. Nature of the Disease

The debate on the nature of Hodgkin's disease was heated during the early part of this century. There was

speculation that Hodgkin's disease was a malignant form of tuberculosis. Both diseases affected the young, often involved mediastinal masses, erratic fevers, night sweats, rash, and weight loss. Sternberg, in 1898, had found the diseases coexistant in eight cases and himself thought Hodgkin's disease to be a peculiar form of tuberculosis. Reed (1902) believed Hodgkin's to be a separate disease but like tuberculosis, inflammatory in nature. In the search for possible infectious agents, the tubercle, diptheria, and brucellosis bacilli as well as several fungi were put forward as possible pathogens. Gordon's experiments in rabbits in which extracts from patient lymph nodes produced acute encephalitis focussed attention on viruses (Kaplan, 1980). Viruses are still under close scrutiny.

The giant cell seen in Hodgkin's tissue was proposed as the Hodgkin's cell by Carl Sternberg in 1898 and by Dorothy Reed in 1902. Reed wrote,

> We believe then from the descriptions in the literature and the findings in the 8 cases examined, that Hodgkin's disease has a peculiar and typical histological picture and could thus rightly be considered a histopathological disease entity (Reed, 1902).

An intermediate view was put forward by Chevalier and Bernard in 1932 who suggested that Hodgkin's disease began as an inflammatory reaction after virus infection with

later transformation into a blastoma. It was not until the Sixth Revision of the International Lists of Diseases and Causes of Death, published in 1948, that Hodgkin's disease was included in the section on neoplasms. Pathologists today still describe the condition as one incorporating elements of both neoplastic and inflammatory disease. Kaplan and Smithers proposed in the late 1950s that Hodgkin's disease might represent an autoimmune process in which antigenically abnormal neoplastic cells stimulated the production of lymphoid cells (Kaplan and Smithers, 1959; Smithers, 1959). Cytogenetic studies (Seif and Spriggs, 1967; Fukuhara and Rowley, 1978) demonstrated that the giant cells of Hodgkin's disease could be aneuploid and clonal, two attributes of neoplastic cells.

Hodgkin's disease was the first of the lymphoreticular neoplasms to be described. Cases of leukemia had been reported by Virchow, Bennett, and Craigie in 1845 but description of the whole of the group of quite different leukemias was not undertaken until much later. Dreschfeld in 1892 and Kundrat in 1893 described aleukemic leukemia or lymphosarcoma, in which neoplastic cells remained confined for long periods of time in the lymphatic system. Reticulum cell sarcoma and the follicular lymphomas were defined, for example, by Brill, Baehr, and Rosenthal in 1925, Symmers in 1927, Oberling in 1928, and Roulet in 1930 (Kaplan, 1980). The most recent addition to the group,

Burkitt's lymphoma, was investigated in Central Africa and later described by Denis Burkitt (1958).

The variation in cell type, in age and sex, and in the natural history of this group of diseases is considerable but the malignant growth of most lymphomas begins in cells which form part of the immune system. Children and adults with one of the inherited or acquired immunodeficiency conditions are more likely to develop a lymphoma as are transplant patients who have had their immune systems artificially suppressed (Penn, 1976).

3. Histopathology

The first histopathologic classification of the different types of Hodgkin's disease was developed by Jackson and Parker and published in 1944 (see Table 5 of the Appendix, p. A-19). They called the main body of cases Hodgkin's granuloma and the more malignant form which is characterized by large numbers of pleomorphic and anaplastic Sternberg-Reed cells, Hodgkin's sarcoma. The term Hodgkin's paragranuloma was then assigned to that other less frequent group of cases in which there were few Sternberg-Reed cells, a great number of lymphocytes, and in which the clinical course proceeded quite slowly. In 1966 Lukes, Butler, and Hicks separated nodular sclerosis from mixed cell disease within the granuloma group, divided paragranuloma into lymphocytic/histiocytic diffuse and

lymphocytic/histiocytic nodular, and sarcoma into diffuse fibrosis and reticular. Later in the same year this classification was simplified at the Rye, New York conference. The Lukes lymphocytic/histiocytic diffuse and nodular groups in which lymphocytes and histiocytes or both were abundant were combined to form the lymphocyte predominant category. The diffuse fibrosis and reticular types in which either lymphocytes and histiocytes or both were sparse were combined into a category designated lymphocyte depletion. Nodular sclerosis and mixed cellularity remained as separate groups. This classification of four categories or types was called after the Rye conference and is still in use (Kaplan, 1980).

The difficulty in histopathological diagnosis stems from the variable appearance of the lymphoid tissue found in Hodgkin's patients. The pleomorphic cellular proliferation and obliteration of lymph node architecture occurs in other diseases. Infectious mononucleosis, post-vaccinial lymphadenitis, angioimmunoblastic lymphadenopathy, and Lennert's lymphoma may present the same nodal appearance. Specimens from these diseases often have more features of immunologic stimulation however, and may or may not contain Sternberg-Reed cells (Neiman, 1978).

In all forms of the disease, definitive diagnosis requires that the Sternberg-Reed cell be found. In its most typical form this is a large multinucleated or

binucleated cell with very large nucleoli. Because similar mononuclear cells can be seen in biopsy specimens in other lymphadenopathies and because Sternberg-Reed cells have been reported by Lukes and others in infectious mononucleosis (1969) and by Strum (1973) in rubeola, thymoma, cancers of the lung and breast, melanomas, mycosis fungoides, Burkitt's lymphoma, and chronic lymphatic leukemia, the occurrence of Sternberg- Reed cells is a necessary but not sufficient condition for diagnosis. The appropriate cellular background must also be present: lymphocytes and histiocytes in lymphocyte predominant and mixed cellularity disease, anaplastic variants in lymphocyte depletion disease, and lacunar cells in nodular sclerosing disease.

Several major pathology reviews have emphasized the difficulties of the histopathological classification of Hodgkin's disease. Symmer's classic paper (1968) reported the results of a review of 600 cases diagnosed between 1947 and 1966. There was confirmation of only 53 percent of the diagnoses. The most frequently confused condition was chronic non-specific lymphadenitis. Reticulum cell sarcoma, infectious mononucleosis, toxoplasmosis, and early sarcoidosis were also frequently diagnosed as Hodgkin's disease. Of the misclassified cases those still considered doubtful after review were all histologically pleomorphic lymphoreticular disease. On the other hand, 85 specimens

referred with other initial diagnoses, usually one of the diseases mentioned above, were eventually labelled Hodgkin's disease.

Interobserver and intraobserver error in classification of Hodgkin's disease was described for over 300 cases by Coppleson et al. (1970). Two of three observers agreed in over 90 percent of cases, regardless of classification. There was unanimous agreement in three quarters of cases typed by the Jackson and Parker classification. Using the Rye classification, there was unanimous agreement in half of the series. Lymphocyte depletion was hardest to classify. When a sample of previously reviewed material was reintroduced to the same observer, disagreement on the diagnosis of Hodgkin's disease occurred only six percent of the time.

Nearly 300 cases of Hodgkin's disease diagnosed at institutions participating in a cooperative clinical trial were reviewed by the hematopathology panel of the Southwest Oncology Group (Miller et al., 1982). Thirteen percent were misdiagnosed as Hodgkin's disease. These were reviewed for the kinds of mistakes made. Most of the cases had been confused with other lymphomas, especially large cell lymphomas with pleomorphic features and Sternberg-Reed cells. Lennert's lymphoma and angioimmunoblastic lymphadenopathy were also confused with Hodgkin's disease. Most of the misdiagnoses had been reported as mixed

cellularity and lymphocyte depletion. Nodular sclerosis was least frequently mistaken.

In conclusion, Hodgkin's disease is accepted by most pathologists as a separate disease entity although its diversity of histological appearance ranges from that of a benign inflammatory response to that of the most anaplastic of carcinomas. Its malignant character is difficult to substantiate. Techniques now available and capable of demonstrating neoplastic growth in other tumors have not been overwhelmingly successful in Hodgkin's disease and several others of the lymphomas. Still, in general, clinical and academic groups accept Hodgkin's disease as a malignant disease.

4. Clinical Presentation

The clinical features of Hodgkin's disease were well described by the turn of the century. Kaplan (1980) has reviewed data on clinical presentation from several published studies.

Over 90 percent of cases present with lumps, masses, or swellings, usually painless. The majority of these are cervical nodes followed in frequency by axillary nodes and inguinal nodes. Occasionally a patient will have felt an abdominal mass. Onset is often sudden but occasionally cycles of swelling will have occurred over several years. Constitutional symptoms are mentioned at presentation with

varying frequency. Fever occurs in about a quarter of patients. It is usually a low grade fever but is sometimes the high cyclical fever described by Pel (1887) and Ebstein (1887). The fever usually occurs with night sweats which may be very severe and are sometimes the only presenting symptom. The majority of patients experience pruritis sometime during the course of the disease. It is occasionally the only symptom and may present diagnostic problems because of its occurrence with other dermatological conditions. Pain in an affected node after alcohol intake is one of the more dramatic presenting symptoms. It is specific for this disease but has been reported in only two to 15 percent of patients in a number of series. There may also be symptoms which relate to hematologic complications such as autoimmune hemolytic anemia and thrombocytopenic purpura. Anorexia, malaise, weakness, and weight loss have also been reported (Kaplan, 1980).

5. Treatment

The introduction in 1950 of a clinical staging classification by Dr. Vera Peters of the Princess Margaret Hospital, Toronto (Smithers, 1973), focussed attention on diagnostic evaluation. Further advances came as new techniques were developed. Kinmouth in 1952 reported on lower extremity lymphangiography which allowed visualization of the pelvic and retroperitoneal lymph

nodes. Tomography and bone scans have further improved diagnostic evaluation. Laparotomy with biopsy of splenic, para-aortic, and mesenteric nodes and the liver, combined with splenectomy came into use in the 1960s (Kaplan, 1980).

Therapy was purely symptomatic until the turn of the century when Pusey in 1902 and Senn in 1903 achieved dramatic results with the very new x-ray. With increasingly sophisticated equipment and techniques it was possible to direct large doses of x-ray therapy to well defined regions of nodes. Surgery, which was used extensively from the 1920s to the 1950s, is now rarely performed; its effectiveness was difficult to evaluate in isolation from subsequent x-ray therapy (Kaplan, 1980).

In the 1940s, through research on the mustard gases used during World War I, it was discovered that nitrogen mustard was a strong cytolytic agent. Subsequently other drugs with similar actions and two other groups, the antimetabolites and the steroids, have been developed. Several chemicals can now be combined and interspersed with cycles of radiotherapy to produce indefinite remission of Hodgkin's disease (Kaplan, 1980).

6. Survival

With the introduction of more accurate staging procedures and new methods of treatment, survival has

steadily increased. Survival varies by sex, age, stage at diagnosis, and histologic type. Females generally have a better prognosis than males. This is partly because they more often have the histologic types with higher survival rates. The young adult survives longer than either the very young or the very old patient. The prognosis for stages I and II is generally better than for stages III and IV. Improvement in survival in Hodgkin's disease has been so dramatic, particularly in asymptomatic patients, that development of further treatment options has been made difficult by the very long observation periods now needed for assessment (Kaplan, 1980). For example, in 346 patients diagnosed between 1966 and 1977 at Massachusetts General Hospital, five year survival for stages I and II increased from 84 to 96 percent; from 20 to 100 percent for stage IIIA; from ten to 80 percent in stages IIIB and IV; and from 58 to 94 percent for all stages (Aisenberg et al., 1979).

Patients presenting with constitutional symptoms die earlier than those who were asymptomatic at presentation (Korst et al., 1973). Lymphocyte predominant and nodular sclerosing Hodgkin's disease have the highest survival rates. Mixed cellularity has a shorter survival in most series and lymphocyte depletion has a very poor prognosis (Brodie et al., 1974; Crum et al., 1974; Nordentoft et al., 1980).

In some patients there have been complications of treatment (Aisenberg et al., 1978; Nordentoft et al., 1980). Radiation has induced bone marrow aplasia and spinal cord injury but also hypothyroidism and temporary or permanent sterility in males. Three percent (23 cases) of Nordentoft's Danish series died of complications of treatment including infection from laparotomy, pneumonia after splenectomy, cardiac arrest during treatment, and hemorrhage after chemotherapy.

7. Multiple Primaries

Although the total dosage of radiotherapy has not changed drastically over the years, the body volume irradiated has increased. The risk for subsequent primary malignancies is particularly high in young people who now have long life expectancies (Brody and Schottenfeld, 1980). In following patients from the Connecticut Registry, the National Cancer Institute, the Italian Cancer Institute, the French Cancer Hospitals, the Memorial Sloan-Kettering Institute, the Southwest Oncology Group, and Stanford University Medical Center, and in data from the Third National Cancer Survey, the cumulative percent of patients diagnosed in the mid-1960s who developed second multiple primaries within ten years of initial therapy was 7.7 percent. Kaposi's sarcoma, soft tissue sarcoma, acute myelocytic leukemia, and non-Hodgkin's lymphoma were most

frequently diagnosed although second primary sites included pharynx, testes, prostate, colon, cervix, melanoma, caecum and oral cavity. Newell et al. (1974) found the risk of second primaries lower in blacks.

It is fairly certain that most subsequent primaries are due to delayed effects of treatment. There are reports of second neoplasms in apparently radiosensitive individuals (Li et al., 1981). Results have not yet been published from several large series of Hodgkin's patients who have had chromosome analysis and who are being followed for development of subsequent cancers.

B. FAMILIAL CASES OF HODGKIN'S DISEASE

1. The West Coast Family

One of the largest familial aggregations of Hodgkin's disease reported in the literature was on the west coast of Newfoundland. In a large kindred descended from one couple, a number of lymphoreticular malignancies, embryonic tumors, and immunodeficiencies were diagnosed over a 20 year period (Buehler et al., 1975). The first case was a young girl diagnosed in 1954 at age seven. Six other cases, all males, were diagnosed from 1965 to 1973 at ages eight, ten, 12, 20, 31, and 60. Three lymphosarcomas, a malignant and a benign thymoma, three leukemias, a neuroblastoma, and a retinoblastoma also occurred in this family during the period 1960-1975. Two rhabdomyosarcomas were

diagnosed. The first was in 1964 in a 20 year old male; the other was in his brother at age 39 in 1978 (Marshall et al., 1980).

There were three common variable immunodeficiencies (CVI) in this kindred. One immunodeficient patient, who remains asymptomatic despite pathologically low values for IgG, IgM, IgA, and IgD, was diagnosed during a field clinic. A second case was the proband of the study and the third was a case who had had repeated attacks of bronchitis and pneumonia, herpes keratitis, and eczema. The proband developed common variable immunodeficiency at age 30 and would now be diagnosed as having acquired immunodeficiency syndrome, AIDS (Marshall et al., 1977).

Twelve hundred people in three small communities were examined in field clinics in 1974 with follow-up clinics in 1975 and 1976 (Crumley, ed., 1973; Marshall, ed., 1975).

Eighty-five percent of the residents of the three communities were descended from a founder couple who arrived on the coast in 1830. Genealogical analysis of the pedigree showed closer degrees of relationship between Hodgkin's patients and immunodeficiency patients than among the Hodgkin's patients themselves. Inbreeding coefficients were high; most patients were descended from the founder couple through both parents (Salmon et al., 1980). Recent analysis by Thompson (1981) has demonstrated the mathematical likelihood of a recessive gene being transmitted to

all Hodgkin's and immunodeficiency patients from the founder couple.

A number of genetic markers were tested for in a community survey; several rare variants were present in the population and several rare associations of markers were found. There were twice as many Rhesus negative individuals in the extended family as were expected (Arnason et al., 1977; Carter et al., 1976; Carter et al., 1978; Larsen et al., 1978; Newton et al., 1979).

Over 600 members of the kindred have been typed for HLA antigens. No single haplotype or antigen could have been shared by all patients but B18 was increased in frequency in first degree relatives of patients. Marshall has suggested that these B18 relatives may be asymptomatic carriers of an infective agent (Marshall et al., 1977).

Tuberculosis was very frequent in the area up to 1960. The incidence of tuberculosis was inversely related to Hodgkin's incidence. The human leucoyte antigen (HLA) B8 which was infrequent in Hodgkin's relatives, was significantly correlated with a history of tuberculosis (Selby et al., 1978).

Elevated IgM was found in the relatives of immunodeficiency patients (Salimonu et al., 1979; Salimonu et al., 1980). IgD levels in the study population were higher than levels in controls from outside the study communities; levels were highest in patient relatives.

In summary, significantly more HLA B18 and Rhesus negative individuals were found among patient relatives than in controls. The decreased frequency of tuberculosis in the community with the highest proportion of Hodgkin's patients is intriguing. Finally, Thompson (1981) has shown that all cases could have received a recessive gene from the founder couple.

There may be a genetic susceptibility which leads in some individuals to Hodgkin's disease and in other family members to immunodeficiency, or the susceptibility may lead first to a subclinical immunodeficiency and subsequently in some individuals to Hodgkin's disease and in others to acquired immunodeficiency. Finally, the inherited vulnerability may produce subclinical immunodeficiency in a number of family members, immunodeficiency of the AID sort in a few, and require the stimulus of an infectious agent for transformation to lymphoma in still others. Although HLA B18 and Rhesus negative individuals in the West Coast communities are at greater risk of having a close relative with Hodgkin's disease or immunodeficiency, no linkage of these factors with disease has been shown in patients in this study.

2. Reports in the Literature

The occurrence of more than one case of Hodgkin's disease in a family suggests that inherited factors may

play a part in the etiology of the disease. Reports of familial cases are documented back to 1886 (Mazar and Straus, 1951) and continue to the present day (Haim et al., 1982), nearly a hundred years later. With our present knowledge of the relationship of immunological abnormality and subsequent risk of lymphoreticular malignancy, the occurrence of multiple cases of any lymphoma or abnormal immune function in a family whether separately or in combination, is of interest. Such reports, particularly of immunological and malignant disease in the same family strengthens the hypothesis that Hodgkin's occurs in families because a susceptibility - an impairment of the immune system - is inherited. The mode of inheritance may differ in different families, making a family member susceptible to an external agent for all or part of his life. These reports as a group are an important aspect of the epidemiology of Hodgkin's disease. Such accounts are not found for all cancers and their continuing accumulation in the case of Hodgkin's disease, disregarding the anecdotal nature of many, cannot be ignored.

Devore and Doan's (1957) now classic study reviewed all familial cases of Hodgkin's disease reported in the literature up to that time. They themselves reviewed 440 single cases treated in Ohio and Oklahoma; sixteen of the patient families had multiple cases of Hodgkin's disease.

Four were sibling pairs and five were parent-child pairs. Seven others involved second degree relatives.

Shortly after this paper by Devore and Doan, Razis (1959) wrote a review article on familial Hodgkin's disease, and further, compared familial cases in five disease groups; Hodgkin's disease, lymphosarcoma, leukemia, malignant tumors of other kinds, and benign disease. Case histories in the five groups were studied for mention of first degree relatives with Hodgkin's disease, lymphosarcoma, or leukemia. The highest rate of familial occurrence was in Hodgkin's patients. The increased risk for first degree relatives was about three times that of a person in a non-Hodgkin's family. The proportion of Hodgkin's probands with a first degree relative also diagnosed as Hodgkin's was about one percent or the same proportion found in breast, uterine, stomach, and esophageal cancer families.

Ninety-two families with at least one leukemia or lymphoma patient and 69 control families were interviewed by Rigby et al. (1966). Twenty-one of the 92 families had multiple cases of lymphoma. In four families with a Hodgkin's disease proband, the second case was Hodgkin's disease.

These were the first descriptions of families with multiple cases of Hodgkin's disease. Such reports, including that from the West Coast, continue to the present time.

Some have documented the family relationships, dates of onset, and histological types; others have tried, in addition, to find blood markers which might predict the susceptibility of a family member.

Potolsky's report in 1971 was one of the first to describe multiple malignancies and immunologically related disease. He was also one of the first to follow the clinical investigation of affected family members with laboratory tests. In a sibship of 12, two had died in infancy, five had died of lymphoreticular malignancy, and one of breast cancer (Potolsky et al., 1971). A number of immunologic, cytogenetic, and virologic tests were done. The four surviving sibs had abnormally low values of IgG; two were low in IgA. One was also low in IgM and another had abnormally high levels of IgM. Delayed hypersensitivity was depressed in all sibs. Chromosomes were normal in all with no evidence of increased breakage. Similar laboratory findings had been reported in 1969 by Fraumeni in the surviving children of a family in which three of 11 sibs had chronic lymphatic leukemia.

Creagan and Fraumeni (1972) described three cases of Hodgkin's disease diagnosed in a family within a three year period. Idiopathic thrombocytopenic purpura was present in two of three cases. An Amish family in which two brothers had Hodgkin's disease was reported by Maldonado et al. (1972). Three Amish cousins with Hodgkin's disease were

described by Halazun et al. (1972). The children shared a common set of great-grandparents. One child lived in another state and had never met his cousins. Consanguinity was also evident in the pedigree of a large Swiss kindred (Hardmeier and Relstab, 1975) in which there were cases of Hodgkin's disease, malignant lymphoma, reticulum cell sarcoma, and malignant melanoma.

In another large family with multiple lymphoma cases, increased levels of IgM with elevated Epstein-Barr virus antibodies, and impaired lymphocyte function were found in three family members (Fraumeni et al., 1975). Lynch et al. (1976) described a large kindred in Nebraska in which there were three cases of Hodgkin's disease and a number of other malignancies, including lymphomas. Occurrence of other cancers in families with a case of Hodgkin's disease was investigated in a case control study in Nebraska (Rosenlof et al., 1971). The occurrence of cancer in multiple case families was 50 percent higher than in two groups of control families (single case families, lung cancer families). Multiple myeloma, Hodgkin's disease and acute myelocytic leukemia were diagnosed in a husband, wife and son over a three year period (Kyle et al., 1976).

Large series of patients have been reviewed for multiple cases (Lickiss et al., 1977; Haim et al., 1982; Greene et al., 1979; Hors et al., 1980). The majority of familial cases of Hodgkin's disease were in siblings.

Often they were diagnosed within a very short period of time. Two brothers were diagnosed within a one month period (Olisa et al., 1973), a sister and brother within two months (Chrobak et al., 1976), two sisters within 18 months (Bowers et al., 1977), and three siblings within one month (Torres et al., 1980). In all of the above families, the siblings were of the same histopathologic type, nodular sclerosing, except in the latter group of three very young siblings aged ten, six, and five who were all mixed cellularity.

Short intervals between dates of diagnosis suggest major involvement of an environmental agent in the etiology of a disease. Similar ages at diagnosis, on the other hand, indicate the role of a genetic component. Razis (1959) was the first to report the relatively short intervals between dates of diagnosis compared to ages at onset which suggested the effect of an environmental factor most likely interacting with genetic components. Vianna et al. (1974) reported that familial cases tended to be younger at diagnosis, sib pairs were more often of the same sex and more frequently had the same histological type, and they were usually diagnosed within five to ten years of one another regardless of age. The records of familial Hodgkin's cases were collected from tumor registry files and the files of previous hospital surveys. Cases were categorized by those who had lived in the same household

before and after diagnosis and those who had lived in different households but in the same county. The majority of cases were under the age of 40. In seven of the nine sib pairs, the interval between diagnoses was shorter than the difference in ages at diagnosis. In the group living in different households, the interval between diagnoses was four times longer than for pairs living in the same household. In the seven sib pairs for which information was available, four were concordant in histologic type. Vianna's method of comparisons over a finite time period was subsequently criticised (Mantel and Blot, 1977) because it allowed observation of short intervals but eliminated the possibility of observing very long intervals, particularly in patients widely separated in age at diagnosis. For instance, few parent-child pairs would be picked up with a 20 to 25 year interval between diagnoses.

Abnormal immune responses have been found in a number of Hodgkin's families including the Newfoundland family. Three sisters in a sibship of five were diagnosed as Hodgkin's disease over a period of six years (McBride and Fennelly, 1976). Two were nodular sclerosing type and the third was mixed cellularity. Recurrent herpes labialis was found in a fourth sister. There was a familial depletion of T lymphocyte function and abnormally low values of lymphocyte transformation. The mother and an unaffected daughter who had had infectious mononucleosis two years

previously, were consistently anergic to skin testing; the mother also had asymptomatic paraproteinemia. The mother of the index case of the west coast family also had an excess monoclonal antibody without symptoms.

Four of five daughters in a Swiss family were affected with malignant lymphoma. The first was diagnosed at the age of 31 as nodular sclerosing Hodgkin's disease (Nagel et al., 1978). Four weeks after her death, a second sister who had helped to care for her was diagnosed as Hodgkin's disease, nodular sclerosing. A third sister living and working in Ghana was diagnosed six years later, as lymphocytic depletion Hodgkin's. The fourth sister had visited Africa at the time the third patient was diagnosed. A year later she was diagnosed as reticulum cell sarcoma. The fifth sister was unaffected. A paternal uncle and second cousin had Hodgkin's disease. All of the sisters had lived at home up to the age of 20.

Typing lymphocytes for the presence of histo-compatibility antigens is increasingly used in a number of diseases, including Hodgkin's disease, in an attempt to find a marker which will distinguish susceptible from unsusceptible individuals. Certain antigens have been shown to be in increased frequency in patients with Hodgkin's disease although a single antigen has not been found in all cases. Particular antigens may be associated only in particular families but even this would enable

prediction of persons at risk in that family. Honeyman and Menser (1975) suggested that certain HLA antigens may mark an increased capacity to acquire the unknown infectious agent of Hodgkin's disease with subsequent spread to contacts. The majority of cases would have only limited ability to serve as 'spreaders'. Marshall has suggested that B18 relatives might have served as spreaders in the west coast family.

Familial Hodgkin's disease occurring with an apparent familial radiological sensitivity was described by Li et al. (1981). The first sister was diagnosed as Hodgkin's disease at age 40; the second sister was diagnosed at age 30. Both were successfully treated. Four years and 11 years after their Hodgkin's diagnoses, the sisters were found to have cancer of the breast. The son of a third sister with breast cancer was exposed to exogenous female hormones in early gestation and developed medulloblastoma at age five. The paternal grandmother, great-aunt, and a second cousin all died of breast cancer. The authors suggested a genetic predisposition to breast cancer enhanced by the carcinogenic effects of radiation. There were no apparent chromosomal abnormalities in the affected sibship.

In summary, the familial occurrence of Hodgkin's disease alone or in combination with other malignancy or immunological abnormality has been described many times.

The risk for a first degree relative of a patient is at least three times greater than for the average person. The first degree relative is most often a sibling and often a sibling of the same sex. Histological subtypes are frequently shared. Dates of diagnosis are commonly close together, particularly in siblings. None of the variables investigated thus far can be associated with cases alone. In nearly every family there are members who share, for instance, the HLA type but remain perfectly healthy.

The role of the familial component of Hodgkin's disease is not clear. However, the many reports of multiple cases of Hodgkin's disease in a family must be considered an important body of information. Although genetic markers are shared by affected members in some families, no simple genetic interpretation is possible. The increased risk of same sex siblings and the proximity of dates of diagnosis argue for an environmental component. Of the hypotheses proposed earlier for the west coast family, that suggesting a genetic susceptibility requiring an external stimulus for transformation to malignancy seems most plausible.

C. THE EPIDEMIOLOGY OF HODGKIN'S DISEASE

1. Introduction

Shimkin (1955) examined U.S. data for Hodgkin's disease mortality from 1921 to 1951. The death rate for

Hodgkin's disease had increased steadily from 0.7 in 1921 to 1.7 per 100,000 in 1951 with sharper increases in the first two decades than in the last. There was a shift toward higher female mortality in the latter part of the thirty year period and towards lower mortality in young males. The overall ratio of males to females was high and death rates were generally higher in whites than in non-whites. This early paper drew attention to two themes that have been repeatedly observed elsewhere, one, that Hodgkin's disease incidence rises with increasing affluence, and two, that the pattern of occurrence by age groups and by sex changes as incidence increases.

In 1957 MacMahon at Harvard University published the first comprehensive paper on the epidemiology of Hodgkin's disease. He used the clinical and pathological records of 546 white residents of Brooklyn, New York who had been diagnosed between 1943 and 1952. The average annual incidence rate was 2.2 per 100,000. This paper was the first to point out the bimodal incidence curve; when age-specific rates were plotted, a peak occurred at ages 25-29 and another occurred at ages 70-74. Bimodality was also seen in the age-mortality curve. Incidence rates were higher in males in all age groups but were more striking in older age groups (over 40 years) and in the very young (0-9 years). Incidence and mortality in blacks were lower than

expected except in the youngest age group. About one and a half times more Jewish than non-Jewish persons died from Hodgkin's disease in the over-forty group; in the 0-39 year old group mortality was greater in Catholics.

McMahon then reviewed death rates published from 15 other countries and found bimodal mortality curves in all but Japan. Although death rates in Japan in the older groups were comparable with other countries, there were almost no deaths in the younger group. He concluded that the differences between the age groups underlying the peaks in the incidence and mortality curves argued for considering Hodgkin's disease separate entities in the young and in the old. The pathological changes in the older group were clearly neoplastic in nature and incidence increased steadily after middle age as it does in most other cancers. In the younger age group the curve was unlike those of other malignant neoplasms and the more malignant forms of the disease were rare.

A second paper by MacMahon (1966) centered on four age groups, 0-14 years, prior to the first mode; 15-34 years, the first mode; 35-39 years between the first and second modes; and over 50 years, the second mode. Most subsequent studies on Hodgkin's disease have used these age groupings in the investigation of this disease. A review of published material including the Ten Cities Survey of 1947 confirmed his earlier findings with relation to incidence,

sex ratios, the lower risk in nonwhites and the higher risk in the older Jewish population. He found that more patients than the general population were in higher social classes, had higher levels of education, and scored higher on intelligence tests. Hodgkin's patients came from the more highly skilled and professional occupations. In the heterogenous clerical group there were 35 percent more patients than expected.

In a subsequent study from Harvard, deaths from Hodgkin's disease in the United States were grouped by age and by the time periods 1949-54 and 1959-61 (Cole et al., 1968). Regions were compared by age-specific mortality curves and by Standardized Mortality Ratios (SMRs) where calculation of expected numbers of cases using the rates of a standard population allow comparison of populations with different age distributions. Hodgkin's mortality in a group of 11 contiguous southern states was comparable to that of other regions of the United States in the middle-aged and older age groups but it was only half that of other areas in the group under 35 years of age. This discrepancy in rates was seen in both time periods but was less pronounced in the latter period; rates had increased as socioeconomic conditions improved. Low rates were also observed in both periods in young adults living in the mountain region. These regional differences in age-specific mortality supported the hypothesis that the two

modes of the age incidence curve resulted from two diseases, not one.

A number of other investigators have examined these two disease groups. Newell (1970) found six primary factors which separated the diseases in the young adult and older groups. They were the extent of disease at diagnosis, the frequency of the Sternberg-Reed cell, the frequency of atypical mitoses, the extent of fibrosis, the frequency of eosinophils, and the amount of preserved architecture. Younger patients more often presented with limited disease of the nodular sclerosing type where Sternberg-Reed cells and eosinophils were frequent, nodal architecture was intact, and atypical mitoses were rare.

When charts of patients over 60 years of age were compared with those of younger patients, Lockich (1974) found that 80 percent of the older patients had presented in stages III and IV and half had symptoms at presentation compared with 47 and 18 percent in the younger controls. Nearly 90 percent of the study group were classified as mixed cellularity or lymphocyte depletion and survival averaged only five months. Both Lockich and Clarke (1973) found retroperitoneal, infradiaphragmatic, and gastrointestinal involvement more frequent in the elderly; mediastinal involvement was less frequent. Clarke used the presence or absence of mediastinal abnormality to separate into two groups 400 patients who had died of Hodgkin's

disease in Ontario between 1960 and 1967. The age-mortality curve of the mediastinal group who were mostly young, was very similar to that of tuberculosis in the early 1900s. For people without mediastinal disease who usually presented with enlargement of other nodes, the curve resembled that found in many neoplasms.

Smithers (1970) had, from the beginning of the two-entity controversy, been more impressed with the well known progression of Hodgkin's disease pathology from lymphocyte predominant to mixed cellularity to lymphocyte depletion disease. If different types could occur sequentially in the same individual, bimodality might simply reflect this progression, not two different diseases. MacMahon replied (1971) that Smithers' data actually supported the two disease hypothesis in that if the nodular sclerosis type is seen mostly in the young and represents strong host resistance as Smithers had suggested, it formed one mode of the disease with age and host resistance simply two more variables which distinguished the two disease processes.

In summary, the broad outline of the epidemiology of Hodgkin's disease was laid down by Shimkin and MacMahon nearly thirty years ago. The duality of the disease is still in question although the two-entity hypothesis is currently in favor. The target for most recent research has been the young adult group.

2. Geographic Distribution of Hodgkin's Disease

a. Patterns

In North America, cancer data is collected and published by several government agencies. New Primary Sites of Malignant Neoplasms published by Statistics Canada was first issued in 1969; this publication became Cancer in Canada in 1976. Statistics Canada acts as a collecting agency for all tumor registry data in Canada. Although Ontario does not yet report for the whole of the province, the data provided in this publication cover most of Canada. Reporting is population based and data are available by political subdivisions. In the United States, on the other hand, large segments of the population are not monitored by any registry. The Third National Cancer Survey (Cutler and Young, 1975) which was preceded by the Iowa Study of 1950 (Haenszel et al., 1956) and the Ten Cities Surveys of 1937 and 1947 (Dorn, 1944; Dorn and Cutler, 1959) provided overviews of Hodgkin's incidence in several areas of the United States. Most of the regions in these surveys were urban Standard Metropolitan Statistical Areas (SMSAs); only two sets of data cover whole states, i.e., Iowa and Colorado.

The international distribution of Hodgkin's disease can be seen in the three volumes of Cancer in Five Continents (Doll et al., 1966; Doll et al., 1970; Waterhouse et al., 1976). Data from the most recent edition have been

used for comparisons with this series (see Section VI, p. 189).

In addition, there have been two international surveys of lymphomas and Hodgkin's disease. In the earlier study, sponsored by the Geographic Pathology Committee of the International Union Against Cancer (1973), lymphoreticular tumors were surveyed in 10 countries. The second study was sponsored by the National Cancer Institute (1973) and concentrated on Hodgkin's disease. Information was gathered on incidence, frequency of histologic types, staging, and survival in the United States, Latin America, Asia, Africa, Western Europe, and Israel.

Using these two important surveys and other published data, Pelayo Correa and Gerald O'Conor described five patterns of incidence for the whole of the lymphoma group: 1) tropical countries with endemic Burkitt's lymphoma and a high incidence of Hodgkin's disease in children (Pattern I; Nigeria, Papua New Guinea); 2) tropical countries without Burkitt's lymphoma but with a high incidence of Hodgkin's disease in children and low incidence in young adults (Pattern II; Peru, Colombia, El Salvador); 3) tropical and subtropical countries with, in addition, high incidence of Hodgkin's disease of the nodular sclerosing type in young adults (Pattern III; Egypt, Singapore, Brazil, Israel); 4) affluent countries with low incidence in children and high incidence of nodular sclerosing

disease (Pattern IV; Norway, United States); and 5) oriental countries such as Japan with low incidence of Hodgkin's disease in all age groups and a high frequency of reticulum cell sarcoma (Pattern V).

Correa and O'Conor later concentrated on Hodgkin's disease alone, outlining four epidemiological patterns. Type I prevails in developing countries and is characterized by high incidence and mortality in males and children, low incidence in young adults, and high incidence in the older age groups. Most cases are mixed cellularity or lymphocyte depletion. Type III has low rates in children and a pronounced peak in young adults which is made up almost entirely of nodular sclerosing Hodgkin's disease. Type II, an intermediate pattern, is found in rural areas of developed countries, in central Europe, and in the southern United States. Type IV is found in oriental populations where there are few cases in any age group. The patterns seem to be closely associated with standard of living.

Much of the international data recently published on Hodgkin's disease have been compared with these patterns. The important epidemiological features of the patterns are the sex and age-specific rates, sex ratios by age, and the frequencies of histologic types.

b. North America

Although tumor registry data covering varying numbers of years have been published for a number of Canadian provinces, there have been no major reviews of Hodgkin's disease for a group of provinces or for all of Canada. A proposal for a collaborative study was circulated by the National Cancer Institute of Canada in the 1970s but this study did not go ahead.

A number of studies in the United States have described the epidemiology of Hodgkin's disease in a particular region. A Kansas study of leukemia and lymphoma found urban death rates higher than rural rates (Martin et al., 1963). The urban-rural variation was confirmed in a California study where deaths in farm and non-farm residents were reviewed by Fasal et al. (1968). Total mortality was similar for the two groups but cancer mortality for all sites was significantly lower in farm residents in both sexes; the SMRs for Hodgkin's disease were 48 in female farm workers and 109 in male farm workers. In contrast, the frequency of deaths from Hodgkin's disease in young adult males was higher in rural than in urban California. Using Mayo Clinic records, Nobrega et al. (1973) found that combined rates for Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma were higher in urban areas of Minnesota than in rural areas.

The Connecticut registry has been used extensively for epidemiologic studies of cancer. It is the oldest population based cancer registry on the continent. The National Cancer Institute, the National Institutes of Health Clinical Center, the M.D. Anderson Hospital in Texas, the Mayo Clinic, and the Stanford University Medical School also have large series of cancer patients. A sample of the Hodgkin's cases registered in Connecticut from 1935 to 1968 were reviewed for age distribution and histologic type (O'Conor et al., 1973) and compared with series from the M.D. Anderson Hospital, Stanford, and the N.I.H. Center. Connecticut and the N.I.H. Center had smaller proportions of nodular sclerosing Hodgkin's disease and larger proportions of lymphocyte depletion disease than did western centers. In a second study incidence and age distribution were reviewed in a series of 1000 cases of Hodgkin's disease diagnosed between 1935 and 1962 and reported to the Connecticut registry (Greco et al., 1974). Age-specific rates were similar to those reported by MacMahon 15 years earlier; the incidence curves were clearly bimodal. The incidence in histologically confirmed cases had increased from 1.3 in 1935-44 to 2.0 per 100,000 in 1945-54 to 2.1 in 1962.

Registry cases from Alameda County, California were compared with cases from the Connecticut registry in a more recent study by Silverman et al. in 1977. Nodular

sclerosis appeared most frequently in both areas in the group under 40 years of age. Both regions showed a Type III pattern but California had higher rates over all age groups and a greater proportion of nodular sclerosis (47 percent versus 40 percent). The authors suggested that Hodgkin's disease in California may be yet another step in the evolution of the Type III pattern. If nodular sclerosis represents host response to a carcinogenic agent or process, then improved nutrition, reduction of chronic disease, and a higher standard of living should improve this response. Further, nodular sclerosing disease should increase with a concomitant decrease in other types of Hodgkin's disease, particularly in children.

In North America, the distribution of cases in the several regions studied fits the Type III pattern. Bimodality of age-specific incidence was evident in most data. Nobrega found a somewhat later than usual first peak in Minnesota (ages 30-39) and Gregario et al. (1982) reported an earlier peak in Kentucky (ages 16-20). Minnesota rates had remained fairly stable over 25 years, while Connecticut rates had increased slightly. Urban incidence was higher in Minnesota and mortality was higher in urban Kansas and California; on the other hand, young adult males in rural areas of California were at higher risk than their urban counterparts. California had the highest proportion of nodular sclerosing disease which may

represent a further evolution of Type III as the standard of living has improved.

c. Europe and the United Kingdom

European studies have centered on Germany and the Scandinavian countries. There have been few papers from the United Kingdom.

An early study of Clemmesen et al. (1952) had shown, even before Shimkin's and MacMahon's work, the higher mortality from Hodgkin's disease in males. When Bjelke (1969) examined morbidity and mortality data for Norway from 1931-55, there were 50 percent more male than female caes and bimodality was apparent. Survival rates were lower in males and in the elderly.

The distribution of age, sex, and subtypes across Europe varied considerably. Stalsberg (1973) reviewed lymphomas using data from the Cancer Registry of Norway. Hodgkin's disease was rare in children with only one case recorded in a child under the age of ten. Although there was a prominent young adult peak in incidence curves, the highest rates were in persons over 60 years of age. Mixed cellularity disease was more frequent in old age, in males, and in rural areas. Nodular sclerosis was more common in younger females, and three times more common in urban areas than in rural regions.

Dorken and Singer-Bakker (1972) found urban-rural differences in Germany similar to those in California with

higher death rates in young males living in rural areas. In a later study looking only at children under 14, Dorken (1975) found the majority living in rural areas. A third of the children had parents working in agricultural occupations.

In a recent Greek study, Floros et al. (1982) found only a third of cases were nodular sclerosing; the majority of these were female. A large proportion of cases were lymphocyte predominant. Only 17 percent of a case series in Sheffield, England was nodular sclerosing Hodgkin's disease (Hancock et al., 1979).

In Portugal, a very poor country, 11 percent of Hodgkin's cases diagnosed between 1930 and 1974 were under ten years of age (Sobrinho-Simoes, 1978). The sex ratio was high, 2.9, and mixed cellularity was the most frequent type (51 percent).

Most European data showed well defined bimodal age incidence curves. Sex ratios were generally low except in Portuguese children. A large proportion of disease was nodular sclerosis in the Scandinavian countries and Germany but this type was less common in Greece, England, and Portugal; mixed cellularity was most common. Urban-rural differences were seen in both Norwegian and German data. Most countries exhibited a Type III pattern.

d. Latin America

Risk of Hodgkin's disease in most regions of South America differs sharply from that in North America.

Nearly half of Hodgkin's cases in Lima, Peru were under 15 years of age (Solidoro, 1966); rates in the older group were similar to those in other countries. Other Peruvian studies confirmed the large proportion of young cases and high sex ratios (Albujar, 1973; Misad et al., 1973). Three fourths of Peruvian cases were mixed cellularity or lymphocyte depletion.

The early peak in age incidence in pooled Argentinian data was seen at age 15, somewhat earlier than in North American data (Besuschi and Ghinelli, 1973). The sex ratio was 5.2 under age 10, dropping to 0.9 in adolescence. On the other hand, in a report from the city of Buenos Aires, the sex ratio was a more usual 1.5 and nodular sclerosing disease was more common (Braylan et al., 1973).

Mixed cellularity was the most frequent subtype in a number of studies from Brazil (Machado et al., 1973; de Carvalho, 1973). In contrast, most Hodgkin's patients in northeastern Brazil had favorable subtypes; incidence was high in both the young and the young adult groups.

In Costa Rica, the sex ratio was 3.0 (Salas, 1973). Half of the Hodgkin's cases in this series were mixed cellularity and within this group, the sex ratio was 4.7.

Correa (1973) and Jimenez (1981) in summarizing Hodgkin's disease incidence in Latin America, pointed out that Peru, Colombia, and Central America had high incidence in children, no young adult peak, and histologic types with a poorer prognosis. Few children presented in Stages I and II. Chile and Argentina had fewer cases in children and a weak young adult peak in the incidence curve. Puerto Rico had an intermediate pattern. There were more childhood cases in tropical countries, in poorer countries, and in countries with a greater frequency of tuberculosis.

e. Middle Eastern Countries

Of the middle eastern countries, Israel in particular has contributed a number of important studies in Hodgkin's disease. Large immigrant populations from Europe, Asia, and Africa permit disease incidence in foreign-born migrants to be compared with first and second generation immigrants.

Hodgkin's incidence in Israelis born in the United States, Europe, and Asia was higher than in native-born residents (Royston and Modan, 1968; Sacks et al., 1973). Sex ratios were low with no significant differences in rates in different Israeli-born ethnic groups (Meytes and Modan, 1969). Mixed cellularity was the most common histologic type in young Israeli adults; nodular sclerosis and lymphocyte predominant types were uncommon in immigrants from Africa and Asia (Sacks et al., 1973).

Abramson (1975) found an increase in mortality in the elderly of all ethnic groups over the period 1950-71 possibly due to increased incidence with longer survival. Mortality was lowest in European-born Israelis and highest in cases born in Africa and Asia. Death rates were the same in those immigrating before and after age 15 inferring little environmental impact on mortality.

Young Lebanese Hodgkin's patients showed the high sex ratios and high incidence rates found in many other poor countries (Azzam, 1966). Sex ratios were also high in India (Grover and Hardas, 1972) and Egypt, particularly in children. Again, mixed cellularity was the most common type; nodular sclerosis had never been recorded for a female at the Cairo Cancer Institute and was infrequent in males (Nasr et al., 1973). Only nine cases of nodular sclerosing disease had been recorded in New Delhi (Dawar and Mangalik, 1978) and 60 percent of patients diagnosed as recently as 1975-78 were clinical stages III and IV (Desai et al., 1982). In an Iraqi series of cases (Yahya et al., 1979), three fourths were mixed cellularity or lymphocyte depletion presenting in stages III or IV.

Israel's native born population exhibited a Type III pattern. Many of the poorer middle eastern countries fell into Type I and Type II patterns. Country of origin was reflected in the risk of disease and histological type of immigrant cases. Age at immigration did not change risk of

death from Hodgkin's disease suggesting place of birth may be important in the etiology of this disease. Nodular sclerosing Hodgkin's disease was extremely rare in India, Egypt, and Iraq, particularly in females. Many patients presented in advanced stages of disease.

f. Africa

Africa is one of the more interesting regions in the international distribution of Hodgkin's disease. The Type I pattern is common; incidence is higher in children and lower in young adults. Both Burkitt's lymphoma and Hodgkin's disease are found in the young; Burkitt's lymphoma is the more common malignancy. The less favorable types of Hodgkin's disease are more frequent and the prognosis in this age group is very poor.

Burkitt's lymphoma accounted for one third of lymphoma cases in Ibadan (Edington and Hendrickse, 1973). Eighty-two percent of the Hodgkin's cases from the Kampala, Uganda registry were mixed cellularity or lymphocyte depletion. Although Hodgkin's disease was rare in children, the sex ratio was nearly 6.0 in this group (Wright, 1973). A later study in Uganda confirmed earlier findings that a large majority of childhood cases were mixed cellularity or lymphocyte depletion; one third of these patients had presented in stage IIIB. The sex ratio was 7.0 (Olweny, 1978).

In South Africa, the sex ratio was also high, 5.0. Most young patients presented with mixed cellularity in stage III or IV disease (Jacobsen et al., 1981). In an earlier study comparing East African and English subtypes, 70 percent of African cases and 58 percent of English cases were mixed cellularity or lymphocyte depletion (Burn et al., 1971).

g. Oceania

Burkitt's lymphoma predominated in Papua New Guinea (Wilkey et al., 1973). Hodgkin's disease was rare but in contrast to other countries, half of the cases in childhood were nodular sclerosis or lymphocyte predominant disease.

Africa and, to some extent, New Guinea, exhibited a Type I pattern of Hodgkin's disease; Burkitt's lymphoma was common while Hodgkin's disease was rare. Childhood rates and sex ratios were high. Generally, children presented with mixed cellularity or lymphocyte depletion disease in advanced clinical stages.

h. Asia

In many malignancies, Japan's incidence patterns are unique; this is also true for Hodgkin's disease. Although rates in older age groups are similar to those found in other countries, the young adult peak is missing.

Three studies have shown a north-south gradient in Hodgkin's incidence in Japan with the highest rates in the south. (Wakasa, 1973; Akazaki and Wakasa, 1974; Tokunaga

et al., 1978). Rates in older age groups have increased over time (Shimizu et al., 1981). Total lymphoma mortality was also high in the southern region, particularly in the small, isolated coastal islands where consanguineous marriages were frequent. A high incidence of Hodgkin's disease has also been reported for Okinawa, another inbred population.

When Anderson (1970) compared malignant lymphoma in Japan, England, and the United States he found Hodgkin's disease the most common lymphoma in the U.S. and England (49 percent); reticulum cell sarcoma was the most frequent lymphoma in Japan (42 percent). Hodgkin's disease accounted for only 20 percent of lymphomas in Japan. The first mode of the Japanese age incidence curve was missing in both sexes and the prognosis was generally poor.

Reticulum cell sarcoma was also the most common lymphoma in Singapore; Hodgkin's disease was rare and usually of the lymphocyte predominant subtype. The sex ratio was high, 5.0 (Tan and Shanmugaratnam, 1973).

Two comparative studies have shown lymphoma incidence in American Japanese to be lower than in American whites but higher than in native Japanese (Haenzel and Kurihara, 1968). Japanese Americans in the U.S. in the over 50 age group have significantly greater mortality than either native Japanese or native Americans (Mason and Fraumeni,

1974). There was no early peak in the age mortality curve for Japanese Americans.

Japan's pattern, Type IV, is unique. Reticulum cell sarcoma is the most common lymphoma. The proportions of this malignancy and Hodgkin's disease in Japan were reversed in North America. Rates in Hodgkin's disease were generally much lower than those seen in North America with lower rates in the north of Japan and higher rates in the south. Rates in U.S. Japanese were closer to those of U.S. whites than to those of native Japanese.

i. Example of Current Geographic Research

One of the more interesting investigations of the last several years looked at socio-economic status, educational level, tonsillectomy, viral antibody levels, and HLA in association with incidence in Sao Paulo, Brazil, a Type II region (Evans et al., 1980; Kirchoff et al., 1980). The study included 70 Hodgkin's patients, 70 control subjects with other tumors, and 128 sibling controls. Incidence in children, particularly in the youngest group, was high with a high sex ratio. Mixed cellularity was the most frequent subtype.

Sibship size, birth order, marital status, occupational exposure, drug usage, exposure to children, and history of viral illness were found not to be associated with risk of disease. Mean sibship size for cases was 7.0; the mean value for controls was 6.6. Current residence and

place of birth of patients were not different from those of controls. Occupational exposure to wood in cases and controls was not different. The number of playmates and the number of children sleeping in the same room at age eight were the same in cases and controls. No differences in the frequency of chickenpox, measles, herpes labialis, hospitalization for viral diseases, or in the age at which they were experienced, were found. There was no seasonality in the month of diagnosis and there was no clustering in schools.

The mean age of patients, 27.4, was significantly higher than the mean age of sib controls, 22.2. Significantly fewer children under 13 years of age were living with a 21 year old Hodgkin's patient than with a 21 year old tumor control. Higher socioeconomic status as determined by occupation and educational level was significantly associated with risk of Hodgkin's disease. Seventeen percent of cases and only seven percent of sibs had had tonsillectomies, a significant difference; the increased risk for tonsillectomized patients was 2.5. However, the overall tonsillectomy rate in this region of Brazil was only 11 percent.

In a concurrent case-control study of viral antibodies in the 70 patients and 230 sibling, parent, and child controls, 30 to 40 percent of Hodgkin's patients showed increased titers of EBV capsid antigen antibody,

approximately the same proportions as reported in the literature for Type III countries. The geometric mean titer of antibody to Epstein-Barr virus capsid antigen was significantly higher in cases than in controls and the proportion of patients with titers greater than 1:320 was significantly greater than the proportion of controls (35.5 percent compared to 2.9 percent). There was an inverse relationship between age and titer.

j. Summary

In few other malignancies has international interest and contribution been so great as it has been in Hodgkin's disease. The combination of age distribution, frequency of histopathologic type, and sex ratio is different in different countries and in different regions of the same country. This variation has focussed attention on the socioeconomic and immunological aspects of the disease. Many recent studies like the one described above, have been conducted within the framework of the geographic patterns of the disease.

3. Risk Factors

a. Hodgkin's Disease in Blacks

Several studies have compared risks for Hodgkin's disease in the black and white populations (Young et al., 1975; Olisa, 1976; Vianna et al., 1977; Cohen et al., 1980). Published rates have been consistently lower in

blacks in both sexes; the rates in young adults come closest to white rates. It is accepted that a large proportion of the black population has been in lower socioeconomic groups and that social class alone may explain most of the differences in rates.

The large increase in lymphoma rates in blacks observed from 1937 to 1971 in data from the Second National Cancer Survey and Third National Cancer Survey may reflect an improving standard of living (Young et al., 1975). Lymphoma rates in U.S. blacks although lower than those in U.S. whites exceeded rates in African blacks by as much as three times.

In studies comparing American and African populations, no distinct peak was seen in young adult blacks and the sex ratios were high. Age incidence curves were those of the intermediate pattern. There were greater numbers of blacks employed as laborers, household workers, and farm workers and fewer in professional and managerial occupations. Histologic types with poor prognosis predominated in U.S. blacks and in both whites and blacks in Africa (Vianna et al., 1977). Nodular sclerosis in blacks was seen almost entirely in males in Johannesburg (Cohen et al., 1980) and there were significantly fewer cases with nodular sclerosis disease in a Washington, D.C. series (Olisa, 1976). The authors suggested that blacks may have less capacity for nodule formation; follicular lymphoma is also rare in this

group. Pattern II seemed to fit Washington, D.C. blacks and the total population of Johannesburg with a bias in Africa toward Pattern I in blacks and toward Pattern III in whites.

b. Social Class

Trends of increasing incidence with improving standard of living have led to more detailed investigations of social class.

In a 17 year followup of 388 cases of Hodgkin's disease diagnosed during World War II Army service, the age distribution, stage at diagnosis, level of schooling, prior occupational class, marital status, presenting signs and symptoms, and survival were reviewed (Cohen et al., 1964). Patients were slightly older than the general Army population and less often married. They had had more education and had more often worked in a middle as opposed to low occupational category prior to service. For those with less than nine years schooling the incidence was 1.5, for nine to 11 years, 2.0, for 12 years, 2.2, and for over 13 years of schooling, 2.8 per 100,000; there was a clear increase in risk with increased level of schooling.

A risk gradient of 2.6 was found in a comparison of the educational level of young Hodgkin's patients with that of the general population (Gutensohn and Cole, 1977). Relative risk ranged from 0.7 in persons with less than

high school graduation to 1.8 in persons with some graduate school.

Hodgkin's cases diagnosed from 1960 to 1972 in Israel were compared with controls matched on country of origin and year of immigration (Abramson et al., 1978). There were no differences in cases and controls in occupational category or social class in country of origin. But risk increased in both males and females in all age groups with increasing level of education.

MacMahon (1966) reported a doubling of risk for Hodgkin's disease from the lowest to highest in England and Wales, 1949-53 social class as inferred by occupation. On the other hand, Alderson and Nyack (1972) found no occupational differences which could be associated with social class in Hodgkin's patients in Manchester, England.

In an analysis of U.S. mortality data, 1950-69, residents of counties with a high socioeconomic status had slightly higher death rates for Hodgkin's disease. Rates were 15 percent higher in males and 40 percent higher in females. The degree of urbanization of the county was not a factor (Hoover et al., 1975).

The ratio of social class 1 (highest) to class 5 overall was 2.3 in a series of Hodgkin's cases and neighborhood controls in California (Henderson et al., 1979). The incidence was 1.5 per 100,000 for class 1, 1.19 for class 2, 1.23 for class 3, 0.73 for class 4, and 0.65 for class

5. The social class gradient was found only in nodular sclerosing disease.

In a Danish study, the school health records of young Hodgkin's patients born between 1930 and 1950 were reviewed along with those of three control groups matched for date of birth, sex, and socioeconomic status (Andersen and Isager, 1978; Isager and Andersen, 1978). The records provided information on height, weight, and birthweight. In general, male Hodgkin's patients were significantly taller than their controls at age 14; female patients were significantly taller than their controls at ages ten and 12. In cases where birthweight was available (33 cases, 99 controls) Hodgkin's patients were also significantly heavier at birth. Because these patients were matched for socioeconomic status, the authors suggested a growth-related risk factor independent of social class and perhaps related to host susceptibility. In an earlier study from Sheffield, England, Hancock et al. (1976) had observed greater heights in Hodgkin's patients in necropsy reports. They confirmed this finding in a followup study of 107 Hodgkin's outpatients matched with 107 other patients visiting outpatient clinics. Hodgkin's patients were significantly taller than controls.

c. Childhood Environment

The geographic distribution of Hodgkin's disease and the increased risk with increasing standard of living

suggested a parallel between Hodgkin's disease and paralytic poliomyelitis. In both diseases age-specific rates vary with economic development. The risk of both diseases is greatest in the very young in less favorable living conditions and in the young adult in more favorable environments. The age peaks in both diseases have shifted over time in the United States as the standard of living increased (Gutensohn and Cole, 1977).

These findings focussed interest on the child's environment, specifically on factors determining exposure to infectious agents. Recent studies have looked at family size, type of family dwelling, and sanitation facilities. Nancy Gutensohn, Phillip Cole, and Sidney Grufferman all, at one time, at Harvard, have been at the center of these studies.

A comparison of Hodgkin's cases with sibling and spouse controls showed an inverse risk with family size (Gutensohn and Cole, 1975). Relative risk ranged from 0.8 in sibships of five or more to 1.6 in sibships of one. In separate studies, Stoopler (1975) and Gutensohn (1977) found similar risk gradients in young patients. Conversely, Vianna and Polan (1978) found increasing risk with increasing sibship size in 90 very young cases (less than 12 years of age) in upper New York state although reanalysis of the data by the Boston group showed no clear trend. There was also no marked trend in the youngest

group in a Portuguese study which included 35 cases under ten years of age. However, most of the youngest patients were from large families which averaged 5.4 children (Sobrinho-Simoes, 1978).

Vianna and Polan (1978) looked at the birth order of their 90 young adult cases and found late birth order cases had half the risk of the cases in the first birth order. The Boston study (Gutensohn and Cole, 1979) had also shown lower risk in low birth orders and a recent Danish study has confirmed this finding (Isager and Andersen, 1978).

The Danish (Isager and Andersen, 1978) and English (Hancock, 1976) studies found cases to have had heavier birthweights and increased heights both as adults and through adolescence, supporting the suggestion of higher risk in children reared in a favored environment. Childhood environment was also investigated in Israel (Abramson et al., 1978). A greater proportion of cases than controls lived in homes with flush toilets and piped water. There was no difference in the number of persons per household.

Using a number of variables such as family size, birth order, single versus multiple family dwelling, level of parental education, number of neighborhood playmates, and infectious disease history, Gutensohn and Cole (1981) interviewed cases and controls and found that young adults who had been reared in small families living in single family dwellings, who had had few playmates and who were

children of well-educated mothers were at higher risk of Hodgkin's disease. Being Jewish and having poorer health care as measured by the number of yearly dental visits, also had some effect on incidence. Being taller or heavier, or having had fewer childhood diseases did not. previous infectious mononucleosis, particularly in females was a definite risk factor; the median interval between the infection and later neoplastic disease was five years. More cases than controls reported having had fever blisters at least three times per year. (see Section III, p. 73) There was no difference in cases and controls in amphetamine use.

In a recent study, Gutensohn (1982) looked at family size, multiple versus single dwelling, and maternal education in three groups of cases and controls, the young adult (15-39), the middle aged (40-54), and older group (over 55). The role of higher social class in increased risk of disease was apparent in the young and middle aged but not discernible in the older age group. Risk among young persons from large families of six or more or who had lived as children in multiple dwellings was half that of persons from the smallest family and of those who had lived in single dwellings. Gutensohn suggested that perhaps the disease in the young was due to a common but late infection while those who contracted the disease in middle age were a

group of susceptibles who were infected as adults, possibly from their children.

In summary, there is consistent association of Hodgkin's disease risk in young adults with their environment as children. Generally, persons who grew up in favorable living conditions within small families were at higher risk. These conditions also reduce exposure to infectious disease supporting the hypothesis that Hodgkin's disease occurs after an age-dependent modification of host response to a relatively common infection, that is, risk of Hodgkin's disease is changed by the age at which exposure to the postulated agent occurs.

d. Tonsillectomy

Tonsillectomy risk has been assessed in many studies. Tonsillectomy is known to be a risk for multiple sclerosis and for paralytic poliomyelitis (Newell, 1970; Benenson, 1975; Gutensohn and Cole, 1977). Risks of subsequent Hodgkin's disease among previously tonsillectomized persons range from 0.7 to 3.6 in a dozen studies.

Vianna is primarily associated with the hypothesis of increased risk with tonsillectomy. In 1971, Vianna and his colleagues investigated tonsillectomy and age at tonsillectomy as risk factors for Hodgkin's disease. If tonsillar tissue is lymphatic, they reasoned, perhaps removal of this nearly complete ring of potentially protective tissue

permits invasion by the Hodgkin's 'agent'. They found the relative risk of developing Hodgkin's disease was nearly three times greater for tonsillectomized cases than for their sibling controls.

This association of risk with tonsillectomy was of obvious interest but the results of subsequent studies were disappointing. A Finnish study compared the frequency of tonsillectomy and appendectomy in Hodgkin's patients to their frequencies in a control series of identical age and sex distribution (Ruuskanen et al., 1971). There was no increased risk for tonsillectomy although the frequencies of both surgical operations were markedly lower in Finland than in the New York counties surveyed by Vianna.

A collaborative study in Los Angeles and New Orleans found almost identical tonsillectomy rates in 176 cases and controls with a relative risk of 1.2 (Newell et al., 1973). Neighborhood controls were used in a California study investigating risk factors for nodular sclerosing Hodgkin's disease (Henderson et al., 1979). The rates of tonsillectomy were the same in cases and controls (48 percent).

Paffenbarger et al. (1977) found no increased risk among persons with prior history of tonsillectomy in a cohort of 50,000 university students of which 44 later developed Hodgkin's disease. A slightly increased risk, 1.3, was found in cases compared with schoolmate controls in Denmark (Andersen and Isager, 1970). Abramson (1978)

reported a similar risk in Israel in a comparison of rates in 403 cases and an equal number of population controls.

In the most recent study of lymphomas, cases of Hodgkin's disease and non-Hodgkin's lymphoma and equal numbers of controls were reviewed for age at onset and prior history of tonsillectomy or appendectomy (Silingardi et al., 1982). There was no correlation between any of the risk factors under study and the subsequent development of Hodgkin's disease. However, tonsillectomized Hodgkin's patients were significantly younger than non-tonsillectomized Hodgkin's patients.

When the role of socioeconomic status was recognized, history of tonsillectomy was viewed as a reflection of higher socioeconomic status and, therefore, a confounding variable. A number of studies controlled for social class differences by using at least one sibling control group, just as Vianna had done in 1971.

The tonsillectomy rate in patients at the National Cancer Institute was slightly higher than in siblings; the relative risk was 1.5 (Johnson and Johnson, 1972). There was no association between tonsillectomy history and clinical features of disease. A similar risk was found in a Boston study comparing young cases and sibling controls (Gutensohn et al., 1975).

Ninety-five cases of Hodgkin's disease under 40 years of age and sibling controls in the same ten year age group

were compared for tonsillectomy history (Vianna et al., 1974). There were more tonsillectomies in cases than controls; the relative risk was 2.0. In same sex siblings, the risk was 3.6. In a subsequent study, Vianna and his co-workers (1980) reviewed previous medical history in Hodgkin's cases and in two sibling control groups. An overall risk of 2.5 was observed for children who had had tonsillectomies. The same risk was observed by Kirchhoff et al. (1980) in Brazil in Hodgkin's patients compared with tumor and sibling controls although tonsillectomy was infrequent in the total population (11 percent). Tonsillectomy was more common in small families in Brazil.

In summary, it is accepted that tonsillectomy varies with social class (Venter and Bloor, 1974) and with local medical practice (Gittelsohn and Wennberg, 1977). But studies controlling for social class by using sibling controls have also found increased risk for tonsillectomy. Risk in countries where tonsillectomy is less frequent than in North America was not increased in one case-control study and increased in another where sibling controls were used. One study found same sex siblings at higher risk.

e. Viruses

Since Gordon's experiments in the 1930s indicated a possible viral involvement, a number of viruses have been

considered as possible agents in Hodgkin's disease (Kaplan, 1980). Herpes viruses have been of particular interest because of their association with animal tumors and with human malignancy. Renal carcinoma in frogs, Marek's disease in chickens, and lymphomas in rabbits and monkeys are all closely associated with herpes viruses. Age, sex, hormonal interactions, and temperature can affect the occurrence of these animal diseases. Marek's disease occurs in both an acute and chronic form. A disease very like infectious mononucleosis can occur in rabbits. The virus in squirrel monkeys can produce a lymphoma, a leukemia, or a benign proliferative disease. In humans, genital herpes virus is being investigated as a cause of cervical dysplasia and cervical carcinoma-in-situ.

The Epstein-Barr virus has been under consideration as an etiologic agent of Hodgkin's disease for over a decade. It has the ability to transform lymphocytes and it is found in the lymphoid tissue of infectious mononucleosis patients alongside Sternberg-Reed cells; infectious mononucleosis and Hodgkin's disease share many epidemiologic features (Evans, 1971). It has also been implicated in another lymphoreticular malignancy, Burkitt's lymphoma. Investigation of Epstein-Barr virus has focussed either on antibody to the virus or on the frequency of Hodgkin's disease in people with a history of infectious mononucleosis.

In a 1973 serological study, antibody titers to Epstein-Barr virus were significantly elevated in Hodgkin's patients compared to clinic, spouse, and sibling controls (Henderson et al., 1974). Titers in lymphocyte depletion cases were about the same as those in controls but were significantly lower than titers in nodular sclerosis and mixed cellularity patients. The highest titers were in the mixed cellularity group.

Other studies have found that Hodgkin's patients had higher antibody titers with levels varying by histological type (Henderson et al., 1973; Hesse et al., 1977; Evans et al., 1980). Hesse et al. (1977) compared antibody titers in untreated Hodgkin's patients with controls matched on sex, age, and social class. Significantly higher titers were seen in patients but only for the nodular sclerosis and lymphocyte predominant groups. Titers were still significantly raised after one year of treatment and after splenectomy.

One of the problems with these studies is the comparison of Hodgkin's patients with healthy controls. Increased antibody titers in immunologically compromised individuals with abnormal lymphocyte populations may simply be artefact. A large scale, long term prospective study such as that done for Burkitt's lymphoma could give unbiassed results. Healthy sera were stored for many years until

sufficient patients were diagnosed to compare their pre-disease serum with that of still healthy controls.

Another way of looking at the possible role of Epstein-Barr virus is to look at the risk of Hodgkin's disease in persons who have had a disease caused by this virus, namely infectious mononucleosis (Evans, 1971). Results have conflicted. In 1973, Robert Miller and Gilbert Beebe of the National Cancer Institute published results of a study comparing the frequency of cancer deaths in a large group of U.S. veterans who had had infectious mononucleosis (IM) during World War II, with an equal number of controls. The men were followed to 1965. Only two Hodgkin's deaths were observed in the group who had had IM; one was expected. In a parallel retrospective study, cancer deaths in a large veterans group were traced back to IM infection during army service; none of the veterans dying of Hodgkin's had had infectious mononucleosis during service.

Connolly and Christine (1974) looked at cases of infectious mononucleosis diagnosed from 1948-64 in Connecticut residents. There were five cases of Hodgkin's disease where only one was expected.

Using national laboratory records in Denmark, all persons who had had a positive Paul-Bunnell test from 1940-1969, over 17,000 persons, were matched with cancer registry records (Rosdahl, 1974). Seventeen cases had been

diagnosed as Hodgkin's disease a year or more after having had infectious mononucleosis; six were expected (relative risk, 2.8). Sixteen of the 17 patients were males and records confirming clinical disease were found for 12. The patients were slightly older at the time of infection than the rest of cases in the Paul-Bunnell registry.

College students at five universities who had had infectious mononucleosis between 1949 and 1969 with confirmation by positive heterophile antibody were matched with a control group of equal numbers (Carter et al., 1977). Both groups were followed through 1974. Three cases of Hodgkin's disease were observed with 1.3 cases expected. No significant increase in any other cancer was found. Diagnosis was, on average, five years after infection. All cases were males and all somewhat older at the time of infection than the majority of IM patients. More of the cases than controls were in upper socioeconomic classes.

A collaborative study from Scotland and Sweden followed patients with serologically confirmed infectious mononucleosis (Munoz et al., 1978). Seven cases of Hodgkin's disease occurred with 1.8 expected, to give a relative risk of 3.5. There were five female and two male cases; the relative risk for females alone was 7.0.

The most recent study of infectious mononucleosis and Hodgkin's disease was in Norway, following patients who had

had postive Paul-Bunnell tests from 1961 to 1972 (Kvale et al., 1979). Patients were followed through 1975. Five Hodgkin's cases, all males, were observed; 1.3 were expected. The relative risk was 2.4.

In summary, virus studies found increased titers to Epstein-Barr virus capsid antigen in Hodgkin's disease patients compared to both family and unrelated controls. They remained increased after treatment and after splenectomy. The titers were generally higher in histologic types with more favorable prognosis. But virus antibody is not found in all patient sera and the genome cannot be found in Hodgkin's tissue.

In the six major studies of infectious mononucleosis discussed above, most of the nearly 42,000 cases of infectious mononucleosis followed were in the young adult group. There was, overall, a three-fold increase in risk among cases who had had infectious mononucleosis compared with those who had not. Diagnosis of Hodgkin's disease was usually within five years of infection. Two studies found Hodgkin's patients were older at the time of IM infection than controls. One of the problems with such studies is the possibility that cases could have had both infectious mononucleosis and Hodgkin's disease at the time IM was diagnosed (Wolfe et al., 1969). However, most of the studies eliminated Hodgkin's patients who were diagnosed less than a year after infection. Hodgkin's disease could

also be a rare sequela to the infection, involving the same etiological agent. The infection may act as a trigger for neoplastic transformation or it could act as a potentiator of a latent disease process or it may simply make the individual temporarily more susceptible to a completely separate agent.

f. Horizontal Transmission

It was Nicholas Vianna with his co-workers in Albany, New York, primarily J. N. P. Davies and Peter Greenwald, who focussed attention on 'clustering' and the possible contagion of Hodgkin's disease.

Almost ten years earlier there had been suggestive reports from Pennsylvania and from Texas. Gilmore and Zelesnick (1962) described a Pennsylvania community where three Hodgkin's and three leukemia cases had occurred over a 13 year period in four families occupying adjoining houses. Two of the Hodgkin's patients were siblings. Two members of the four families had infectious mononucleosis and four members had other cancers involving caecum, stomach, liver, and brain. In a second report, two medical students in Texas were diagnosed as Hodgkin's disease within a six month period (George et al., 1965). They did not room together but one used the apartment while the other was away on vacations. A hometown friend of one student with whom there had been a close association up to departure for university was diagnosed two years later.

Vianna and his colleagues (1971) first investigated several small groups of cases in upper New York state. These eventually coalesced into a large time-space cluster. In the first small group, one of two young roommates was diagnosed as Hodgkin's disease. A classmate of the proband developed the disease a year later. The father of one of the classmate's close friends was diagnosed six months later. Subsequently, a friend of the father and a new roommate of the proband's first roommate were diagnosed. The second group was in a school in downstate New York. The first case was a teacher. The next five cases were students; four had been in classes with the teacher and one was an editor of the school newspaper which she supervised. The third and largest group centered on the 1954 graduating class of Albany High School and involved mainly a clique of friends, some of whom had known each other throughout their school years. In this small group of about 30 persons, plus their family and social contacts, there had been 32 cases of Hodgkin's disease diagnosed over 17 years. The ages of the patients ranged from 14-74. All histological subtypes were involved. With one exception, case-case links or case-contact-case links indicated spread from young to old.

In a followup study, 18 of the first 21 cases of Hodgkin's disease in the high school cluster were matched by age, sex, race, and residence in Albany County to

hospitalized burn victims and to a second control group of high school students. None of the burn control group could be linked to each other directly or through a single intermediary. None of the students could be linked to any lymphoma patient past or present through relatives or social contacts (Vianna et al., 1971; Davies, 1972; Vianna et al., 1972).

Vianna and Polan (1973) then looked at all high schools in Nassau and Suffolk Counties, New York. They predicted that if a Hodgkin's case was present in the 1960-64 period, that that high school would be more likely to have another case in the following 1965-69 period than a school which had had no case in the earlier period. The number of secondary cases expected in schools with an index case was 9.3; 21 cases were observed. Among teachers, 0.9 were expected, the actual number diagnosed was seven. The mean interval between an index and secondary case was 3.8 years.

In the same year, an Ohio cluster was described by Klinger and Minton (1973). Five cases of Hodgkin's disease were diagnosed over a 13 year period in a small rural township, population 1300; a sixth case, linked by family relationship, was diagnosed during this time period but outside the township. Two of the cases and two of the contacts were in school together. A third case had married

one of the contacts and the remaining three cases were interlinked by social or family contacts.

The descriptions of the New York and Ohio clusters and the ensuing controversy which surfaced in the correspondence and short article sections of a half dozen journals through the mid-1970s involved statisticians and epidemiologists in the United States, and England (Davies, 1972; Pike et al., 1974; Pike and Smith, 1974; Smith and Pike, 1974; Smith and Pike, 1974; Vianna, 1974; Vianna, 1975; Vianna, 1976; Smith, 1978). Pike and Smith (Smith et al., 1973; Pike and Henderson, 1975; Smith and Pike, 1976) have been the main antagonists of cluster studies. They criticized the Albany report because suitable controls were not used, and because a certain number of contact clusters could occur by chance. They proposed that a Hodgkin's patient could have 500 yearly contacts in a ten year period prior to diagnosis. On the basis of an incidence rate of four per 100,000, there would be a 20 percent probability of having had contact with another case in that ten year period by chance alone. If the contacts of contacts were considered, i.e., the indirect links, the probability would increase, even if there were fewer than 500 direct contacts. In criticism of the Ohio cluster they pointed out that if the six cases were randomly assigned to townships on the basis of the census alone, after 5000 such simulations, the proportion of times the average annual incidence

would exceed Klinger and Minton's 34.4 per 100,000 rate in any one of the 14 townships would be two percent. If the whole of the United States were divided into Union County-sized units, in two percent of 160 of them one would expect to find situations more extreme than that found by Klinger and Minton, i.e., enough clusters to report one a week for three years.

The publicity on clustering prompted another group of anecdotal reports. These reports, like those of the familial cases, were simply descriptions of aggregations of cases. In total, however, they documented the obvious interest and concern of the researchers involved. Also, reports of clusters are not found for all cancers and therefore have to be considered a part of the total Hodgkin's picture.

Three clusters described in California (Dworsky and Henderson, 1974) involved a husband and wife, a group of seven neighborhood heroin users, and a junior high school teacher and five former students. It is interesting that drug intolerance is seen in some cases of immunoblastic sarcoma (Lukes and Tindle, 1975) and an increased risk of Hodgkin's disease in dexedrine abusers has been reported, also from California (Newell et al., 1973).

Ramsey (1975) reported a neighborhood cluster in Melbourne, Australia. Of the five patients, two lived in

adjacent blocks, two were next door neighbors, and two were also close friends.

One of the most interesting clusters was described by Plouffe and his colleagues (Plouffe et al., 1979; Schwartz et al., 1978). Ten cases of Hodgkin's disease occurred in residents of a small town (population 1250) over a twenty year period. The town was the site of the largest bean and grain storage elevator in central Michigan. During each harvest season much of the northern end of the town was covered with dust. All of the cases worked or lived near the elevator complex. Town residents, including patients and patient relatives, were studied alongside a control group made up of residents from two neighboring communities. Both subjects and controls were screened for malignancies, recurrent infection, and use of aspirin and corticosteroids. Purified phytohemagluttinin stimulation and T-cell rosetting were normal in both residents and controls but lymphocyte stimulation with crude PHA extract resulted in significantly higher counts in residents and were particularly high in two of the four cases. In the other two cases values were similar to those in the non-resident group. Extracts with lectin removed showed no lymphocyte stimulating activity. The authors speculated that perhaps chronic antigenic stimulation such as that provided by the bean dust, initiated malignant change in a proportion of the exposed individuals.

These descriptive reports piqued interest. Two early attempts to search for clusters had produced ambiguous results. Cases of lymphoma and leukemia in Connecticut had been reviewed for one and two year clusters within towns (Ederer et al., 1965). Lymphoma cases tended to cluster while leukemia cases alone, and leukemia combined with lymphoma cases, did not. A year later in a similar study from the National Cancer Institute the numbers of pairs observed for each interval matched the expected frequency (Lundin et al., 1966). The authors concluded there was little evidence for the aggregating of leukemia and lymphoma. Although no statistical method had yet been able to show that any of the reported groups were significant, new studies were undertaken specifically searching for clustering.

Alderson and Nayak (1971) analyzed cancer registry cases from the Manchester region for time-space clustering. The time span was divided into 30 day intervals and space into single kilometers. The only evidence of clustering was seen in patients 15-44 years old who had been registered in the period 1963-64.

Heath et al. (1971) interviewed Hodgkin's patients under 40 years of age who had been diagnosed in the Atlanta, Georgia area from 1968 to 1971. In only two cases were other patients mentioned as contacts. One contact was a fellow worker, the other the classmate of a case who in

turn was a close friend of the parents of another patient. Only one school was attended by more than one patient and those two patients had attended at different times.

In West Virginia, Schimpf et al. (1975; 1976) found that 36 percent of randomly selected Hodgkin's patients had had direct or indirect personal association with other leukemia or lymphoma patients. In a later study, Hodgkin's patients and controls in two census enumeration areas of low mobility were interviewed for information on close personal contacts between cases, controls and cases, and controls. Combining both direct and indirect links, patients had a greater than expected number of links in the one area, but not in the other.

Using Vianna's design, high schools with cases in 1960-64 were matched with schools with no cases in this period, and then compared for the occurrence of cases during the five succeeding years, 1965-69 (Grufferman et al., 1979). The proportions of 'exposed' and 'unexposed' schools with cases in the second time period was the same. 'Exposed' students were followed through 1973; there were 12 cases in this group with 13.9 expected.

Smith's group (Smith and Pike, 1974; Smith, 1978) identified all Hodgkin's patients under 40 years of age resident in Oxford, England and diagnosed in the period 1962-71. Each of the patients was matched to a hospital control; both groups were interviewed to determine times

and places of schooling and work. Links from patient to patient, control to control, and patient to control were established. There was no evidence of excess links between patients compared to controls. All combinations of possible periods of susceptibility and infectivity were examined. Only with the combination of work location as place, and a period of susceptibility of five to ten years prior to diagnosis, and date of diagnosis plus two years as period of infectivity, could any linkage be detected. Seven pairs could then be linked where 2.8 were expected.

The frequency of school attendance links among cases of leukemia and lymphoma was examined in Connecticut high school teachers and students (Zack et al., 1977). There were five teacher cases of Hodgkin's disease and 386 student cases. The proportion of cases among all students enrolled in schools with a previous student case was compared with the proportion of cases in schools without an initial case. A small but statistically significant increase in case-case links was found for Hodgkin's disease but not for non-Hodgkin's lymphoma or for leukemia. Significant increases in risk were also seen in Hodgkin's-lymphosarcoma links. Otherwise there were no differences in socioeconomic indices, median school years completed, or median family income although there were fewer persons per household and less mobility in the districts with cases compared to districts without cases. In a second phase of

the study, using student patients to define exposed cohorts as Vianna had done previously, only Hodgkin's disease was diagnosed more often in exposed than in non-exposed (2.1 relative risk). Cases developing in exposed cohorts were similar in age, sex, year of diagnosis, and high school attendance years. The median interval of onset between linked cases was seven years. In the 15-19 year old group, there was an approximate three fold increase in risk in contacts of patients with Hodgkin's disease.

The scarcity of husband-wife cases is puzzling. If an infectious agent is involved, without a particular susceptibility, a husband and wife should be likely to infect one another. Mazar and Straus reported one spouse pair in 1951 and Berliner and Distenfeld described a second pair in 1972.

If the possibility of horizontal transmission is accepted and husband-wife patient pairs are rare, perhaps the transfer of an environmental factor is better effected at younger ages. Cole has suggested that emphasis be placed on aggregations of exposure and not clusters of occurrence. But one of the problems of investigating aggregations is that one is not sure when effective exposure takes place and whether age at exposure is important. There was no excess incidence of lymphoma in cohorts of young children in Texas and Georgia who had been exposed in utero to influenza virus (Randolph and Heath,

1974). And a Finnish study of the antenatal and delivery records of cases of childhood malignancy found no risk associated with obstetrical history, details of delivery, maternal drug usage or vaccination, or the height, weight, Rhesus grouping, and Apgar score of the child (Ruuskanen et al., 1971). On the other hand, in a study of breast cancer, Boice and Monson (1976) followed women who had had fluoroscopic x-ray for tuberculosis. The women who were at greatest risk of subsequent cancer were in the group aged less than 30 at exposure. In this case, age at exposure was a significant factor in risk of disease.

Seasonal variation in the births of patients also suggests an age-related environmental exposure. Fraumeni and Li (1969) in a study of childhood cancer found a greater than expected number of male births in July and August in Hodgkin's patients. Vianna (1978) also found a greater frequency of late summer births in patients under twelve and in first and second born children.

The clustering of dates of diagnosis supports the role of an environmental exposure. Several studies have shown a greater frequency of diagnoses in cold months. Cridland (1961) found a peak of disease onset in December; coincidental respiratory disease or recent upper respiratory tract infection was not more frequent in this month. Fraumeni and Li (1969) found a greater frequency of diagnoses in children in December and January; Machado

(1973) found an increase in frequency of diagnosis in early autumn in Brazil. But Bjelke (1969) found no seasonal variation in Norway and none was detected in Germany (Dorken and Singer-Bakker, 1972).

In summary, no statistical study designed specifically to search for clustering has produced solid evidence for such a phenomenon. Every a priori cluster can be explained by chance alone. On the other hand, clusters continue to be reported. The interrelationships of the cases and contacts seem to be more than coincidental. In most links, contact comes in a period when the first case could be considered infective and the exposed case susceptible and it precedes diagnosis of the second case. Clusters have been described for Hodgkin's disease and also for leukemia but they are rarely reported for other malignancies. If Hodgkin's disease is in some way contagious it should appear more frequently in persons in close contact such as spouse pairs but it does not. Contact at younger ages may be important although studies of prenatal exposure produced negative results. Why more diagnoses should take place in colder months is not known. One of the most intriguing findings is the seasonal variation of patient births.

g. Occupation

Another way of detecting possible contagion with an environmental factor is to look at the frequency of cases in various occupational groups.

If Hodgkin's disease is contagious the groups expected to be at highest risk would be teachers who work closely with the many school-aged patients and physicians who are closely associated with patients in their treatment. Hoover (1974) and Milham (1974) looked at deaths in male teachers and found a slight excess risk which could be explained by social class alone. Neither physicians or registered nurses were at excess risk in Grufferman's Boston study (1976). There was no increased risk for physicians in Bjorkholm's study in Sweden (1982).

A slightly increased risk, 1.8, was found by Vianna et al. (1974) in upper New York state. Thirteen physicians died of Hodgkin's disease from 1960-72 giving a death rate of 6.9 per 100,000 compared to 3.8 per 100,000 in the general population. In a review of all deaths from Hodgkin's disease in radiologists and radiotherapists, general physicians, opthalmologists, and otolaryngologists, the number of deaths observed was exactly as predicted (Matanoski et al., 1975).

Another exposure which, with only two exceptions, has persistently shown an increased risk for subsequent Hodgkin's disease is exposure to wood.

Milham and Hesser (1967) compared death certificates of males over 25 years of age who had died of Hodgkin's disease in upstate New York with those of matched controls.

Occupations with exposure to wood such as carpentry, sawmill operations, and lumbering were in excess.

A followup of the Milham and Hesser study was done in the Oxford, England area where there was a high concentration of furniture manufacture and a high incidence of Hodgkin's disease. No excess risk was found in occupational groups exposed to wood (Acheson, 1967). This study and the results of an occupational study in Sweden (Bjorkholm et al., 1982) are the two studies which have not found increased risk for woodworking occupations.

An interesting report from Greene et al. of the National Cancer Institute (1978) described a family in which three siblings and a first cousin developed Hodgkin's disease. All of the brothers worked for a fence installation company and routinely used an insecticide/fungicide solution which contained cedar wood products. A fourth unrelated Hodgkin's patient was employed by the same company. In a second phase of the investigation, occupational information contained in North Carolina death certificates was reviewed. Exposure to wood and paper resulted in a relative risk of 1.4. The relative risk was 4.2 within the smaller carpentry and lumbering subgroups.

Petersen and Milham (1974) found a similar association in men who had died in Washington state from 1965-70. Fifty-six deaths were observed; 34 were expected (relative risk 1.8). Men in carpentry and papermaking occupations

were at highest risk. In the Boston occupational study, Grufferman et al. (1976) found a slightly increased risk for persons in woodworking occupations. Fifteen deaths were observed; nine were expected (relative risk 1.6).

Abramson et al. (1978) found no difference in risk for persons in woodworking occupations in Israel compared to other categories (relative risk 1.1). But the association of wood exposure and mixed cellularity Hodgkin's disease was quite strong (relative risk 5.2). A report from France (Andrieu et al., 1979) suggesting an association between localized axillary Hodgkin's disease in manual laborers, noted that the majority of cases were employed in the construction industry.

The number of studies showing excess risk in occupations with wood exposure suggests a real association. Wood dust could be an antigenic irritant as has already been suggested for parasitic infestation, dust exposure, and bacterial and viral infections.

Other occupational exposures have also been reported. In persons over 45 years of age there was a slightly increased risk of Hodgkin's disease for men employed in occupations where benzene, a coal tar derivative and well-known carcinogen, was employed (Vianna and Polan, 1979). As mentioned previously, Andrieu et al. (1979), in a report from France, described 16 cases of Hodgkin's disease diagnosed between 1965 and 1974 with axillary

localizations of disease. Twelve of the 14 patients interviewed were engaged in manual work (86 percent) compared to the 30 percent of all French workers reported as manual laborers in the census statistics. The authors suggested that a genetic factor could be involved which predisposed to transformation after long local modification of lymphatic tissue. However, it could have been that an exogenous agent was allowed entry through the frequent hand sores reported by these men who were mainly employed in the construction industry.

SECTION IV: METHODS

A. DATA SOURCES

1. Death Certificates

a. Historical Development

Registration of death has, from earliest settlement in Newfoundland, been the responsibility of the clergy. In 1538, the clergymen of England were instructed by Thomas Cromwell to keep records of all baptisms, marriages, and burials. Irish clerics received similar instructions in 1600. The first clergy in Newfoundland were transient; they came on ships for the summer fishery and returned to England or to Ireland for the winter months. As permanent settlement began in the early seventeenth century, they gradually immigrated to take up posts in the villages or outports. Reverend Erasmus Stourton of the Church of England was resident in John Guy's colony of Cupids from 1611 to 1628 and three Catholic priests accompanied Lord Baltimore to Ferryland in 1622. The clergy remained under the jurisdiction of their home churches, recording in parish registers all burials, christenings, and marriages performed. Complete registration was impossible; many deaths, for instance, occurred in winter or in the stormy fall and spring months when people dependent on transport

by sea were unable to bring their dead to the nearest clergyman for burial.

In 1890, in an act "to provide for the Registration of Births, Marriages, and Deaths" (53 Victoria, Cap. 21, Nfld, 1890), the Newfoundland government required the clergy in Newfoundland to take responsibility for registration of vital events. Although mention is made of earlier acts in 1865 (28 Victoria, Cap 5, Nfld, 1865) and in 1874 (37 Victoria, Cap. 94, Nfld, 1874), there is no evidence that these were enforced. Volume one of Newfoundland's death registers is dated 1892 (Dewey, 1978) and from then on all information on deaths was sent quarterly by the clergy to the newly established Registry for Vital Statistics.

The first annual report of this registry was published in 1900 with numbers of deaths listed by sex, age, region, and cause. Reporting was incomplete in early years, particularly for the more isolated regions of the province due to loss of records in transit, simple neglect, and in many cases, records being destroyed, usually by fire. Since 1949, when Newfoundland joined the Confederation of Canada, copies of certificates have been sent regularly to Ottawa for coding and tabulation by the Dominion Bureau of Statistics, or, as it is more recently known, Statistics Canada.

b. Current Status

Because of the isolation of much of the population, many people died at home unattended by a professional medical person. With better communication in recent years, the primary diagnosis of most patients dying outside hospital is known and the cause certified by either the local doctor or public health nurse.

The majority of deaths occur in hospital and copies of death certificates are sent from the hospital to the registry. Official return of death is still the responsibility of the clergy. The usual routing of the certificate is from the attending doctor through the admissions and medical records departments of the hospital to the undertaker and finally, to the clergyman in charge of the burial service who sends his completed copy to the provincial registry (see Figure 4 of the Appendix, p. A-5). The hospital copy and the official certificate returned by the clergyman are then matched at the registry. For his services, the clergyman is currently paid fifty cents per return (Dewey, 1978). Newfoundland registers approximately 3000 deaths per year excluding neonatal deaths. The original paper certificates are filed in four binders for the 1000, 2000, 3000 and 4000 series of registration numbers.

Early death certificates requested very little information. At the recommendation of the Newfoundland Medical Association, the provincial Department of Health adopted a new and more detailed death return in the latter part of 1975, effective April 1, 1976. The earlier death certificate and the version currently in use are shown in Figures 5 and 6 of the Appendix, pp. A-6-7. Few forms are completed in full. Personal information, i.e., birthplace, mother's maiden name, and, more recently, additional items such as parents' birthplaces, is most often incomplete. This information is not requested on the majority of hospital forms and is very often unobtainable when no relative is present at time of death. When Ottawa requests the registry to supply more complete information a request is sent to the clergyman or undertaker but no subsequent attempts are made since there is neither staff nor money available at the registry for indefinite followup.

Few post-mortems are authorized (about 20 percent of deaths in the General Hospital, St. John's, in recent years) and these are often performed after the signing of the death certificate. There is no mechanism within most hospitals or within the Department of Health for routinely altering the registered cause of death to match autopsy findings. Therefore, in some cases, the certified cause of death and the final diagnosis at autopsy differ.

Certificates of death are microfilmed within the local registry and sent monthly to Ottawa where they are coded. The microfilm copies and tabulations are then returned to Newfoundland along with alphabetic indices. Final reports to the local registry must be made by March 1 of the year following the report year. The provincial annual report is generally published one year later, i.e. data for 1978 will be published in 1980. The data for the whole of Canada are published in the Vital Statistics series and the Causes of Death series which are released two to three years after the report year.

Finally, it should be noted that all geographic tabulations up to 1974 were by provincial electoral districts. Since that year, the provincial registry has used census divisions.

2. Hospital Records

a. Historical Development

Hospital records presumably began with the establishment of the first hospital in the province, a small military hospital maintained by the French in Placentia in 1662. In June of 1813, the foundation stone of Newfoundland's first public hospital was laid and in 1870, the St. John's garrison hospital was handed over to the colonial government with the first patients being admitted in 1871 (Keegan, 1937). The first cottage hospital in

Newfoundland opened at Old Perlican in January of 1936; the most recent addition to the cottage hospital system, Bell Island, was dedicated in February of 1965. Most early hospital records have been lost through fire and unsuitable storage conditions. Probably the oldest records still in existence are those at the General Hospital, which are in ledger form and which date back to 1890.

b. Current Status

In 1957, the government of Newfoundland required that all hospitals submit admission-separation forms for payment under the newly instituted hospital insurance plan. These forms requested identifying information, admission and separation diagnoses, and a record of all procedures done. It was also in 1957 that the Department of Health began coding all diagnoses according to the International Classification of Disease (ICD) published by the World Health Organization. The return of these admission-separation forms and their coding made possible retrieval by computer of all admissions-separations in the province with a particular diagnosis.

Numbers of admissions are not necessarily equal to numbers of individuals. Admission numbers are unique; one number per admission, or six different numbers for six different admissions. Two admissions in one year for a male aged twenty living in St. John's could be one patient

admitted twice for treatment, or equally likely, two men with Hodgkin's hospitalized during that year.

In 1970, the uniquely identifying number of the Medical Care Plan (MCP) was introduced. This number incorporates a code for the first three letters of the surname (or maiden name, in the case of married females) and a five digit code for date of birth, based on the Julian calendar. The entire number has twelve figures which includes, in addition, codes for sex, twins, and check digits. After the first province-wide assignment of numbers, the MCP number was given only as persons applied directly to the Medical Care Commission. A number of persons in the province were without MCP numbers for some time in the early years of the program and were admitted to hospital without a number.

Through 1970, residence codes were two figure numbers specifying a hospital district. In 1971 these were replaced by a nine-digit number incorporating geographical coordinates which identified even the smallest settlement in Newfoundland.

Central Newfoundland Hospital in Grand Falls, Western Memorial Hospital in Corner Brook, and the Grace Hospital in St. John's have routinely reported patient chart numbers to the Department of Health. The Janeway Hospital began sending them in as soon as it opened in 1968. By 1970 all hospitals except the General Hospital, the major teaching

facility in the province, were submitting chart numbers on admission-separation forms; in 1974 information was complete for this hospital.

Charting systems varied considerably from hospital to hospital and over time. Most hospitals in the province use a "decentralized unit system" in which inpatient and outpatient records are numbered separately. An individual patient's records are kept under one unique number and a sequentially higher number is assigned to each new patient admitted to that hospital. Several hospitals, including the largest institution in the province, have at one time or another, used a "decentralized serial unit system" which assigns the admission number to the chart covering that hospital stay. Consequently, a patient admitted six times in one year had six different admission numbers and, correspondingly, six different chart numbers. Every attempt was made to collect together all charts on an individual patient through a name file but the chance of clerical error and misfiling was greatly increased under this system.

Old files are stored in separate premises in most hospitals; in some hospitals the chart on any patient known to be dead or no longer resident in Newfoundland is microfilmed. Files for each admission are photographed in yet another hospital necessitating scanning several years of microfilm to review all of a patient's previous

admissions. At the children's hospital, all charts for patients who die or who have reached their seventeenth birthday are stored on microfiche.

In 1971, midway through the study period, there were seven major hospitals (over 100 beds each), seven regional hospitals, 16 cottage hospitals, and the four hospitals and 10 nursing stations operated by the International Grenfell Association. These hospitals are shown in Figures 7A and 7B of the Appendix, pp. A-8-9.

There is, at present, no province-wide retrieval of information by diagnosis from the medical insurance data (MCP). Development of such a program is unlikely in view of the cost of a system capable of handling the large volume of records and also because the number of coding staff in the department is barely adequate to maintain the yearly transfer of data from paper to computer tape. The latter problem has been somewhat alleviated in the last four years with the institution in July, 1978 of initial coding at the hospital level with only validation checks at the provincial level. Complete data for any one year is usually available from the hospital insurance division two years after the end of the report year, i.e., in 1982 for 1980 data.

3. Radiation Oncology Records

a. Historical Development

In August of 1945, the Radiotherapy Department of the General Hospital, now known as the Radiation Oncology Department, was opened. This was and is still the only such department in the province. Each patient was assigned a unique number stored on an abstract card along with diagnosis, symptoms, and treatment regimen (see Figure 8 of the Appendix, p. A-10). Each patient also had a filed chart containing the initial history and examination, followup notes, and copies of all laboratory and pathology reports. The department had always made routine followup inquiries to document subsequent treatment and the current status of the patient. Fortunately, from its inception, the department maintained records on all patients referred for consultation whether or not treatment was undertaken (Murphy, 1978).

b. Current Status

All patients in the province requiring radiotherapy and many patients requiring chemotherapy are referred to the treatment center in St. John's. Therefore information is available on most tumors with the exception of those generally treated by surgery alone. The records include the abstract card as well as the more complete notes in filed charts. Up to September, 1978 these records were filed by treatment number, essentially a chronological

file; in October, 1978 the records were rearranged alphabetically by surname within diagnostic categories.

Occasionally patients have been referred to centers outside the province for treatment. They are most often sent to Halifax, Montreal, and Toronto. The radiation oncology department receives copies of all reports on these patients when they are referred back for followup in Newfoundland.

4. Provincial Tumor Registry

a. Historical Development

In June of 1971, the Newfoundland government incorporated, through an act of legislature, the Newfoundland Cancer Treatment and Research Foundation (Statutes of Nfld, 1971, No. 63). Among the responsibilities assigned the foundation were the establishment and maintenance of "adequate reporting of cases of cancer and the recording and compilation of data relating to cancer". These objectives were achieved by the development of a Provincial Tumor Registry administered by the foundation. Official registration began in January, 1974 using the card format recommended by Statistics Canada (see Figure 9 of the Appendix, p. A-11).

In two of the larger centers, Grand Falls and Corner Brook, nurse-coordinators were introduced. These nurses were given responsibility for counselling, assistance at followup clinics, and for conducting educational programs.

They were also to assist in the reporting of new cases of cancer from these areas.

The foundation's annual report, published in the spring of every year, provided listings of all cases diagnosed in the previous year, tabulated by sex, age, site, and census division.

b. Current Status

From January 1974, all hospitals, except the Janeway Children's Hospital, reported new malignancies to the registry. With a change in the Janeway's articles of incorporation, reporting from this hospital began in January, 1978.

The registry staff regularly visit the four hospitals in St. John's and the Radiation Oncology Department to review charts set aside for them by the medical records staffs. The nurse coordinators are responsible for reporting from the central and western Newfoundland regions. Copies of pathology reports from regional laboratories are sent to the registry and are followed up by questionnaires mailed to the appropriate medical records departments. Copies of death certificates where cancer is given as a cause are now sent to the registrar from the Vital Statistics Registry on a regular basis. At irregular intervals, the Department of Health also forwards computer print-outs listing the hospitals and chart numbers of inpatients diagnosed as cancer patients.

The registry reports monthly to Statistics Canada for publication in the series, New Primary Sites of Malignant Neoplasms (1969-1975), or more recently, Cancer in Canada (1976-). This publication is circulated approximately three years behind the report year, i.e. published in 1982 for the year 1979. Information tabulated by Statistics Canada is returned to the local registry on tape one year after submission of the data.

The opening in October, 1981 of the Newfoundland Cancer Clinic which is also administered by the Newfoundland Cancer Treatment and Research Foundation, will lead, in future, to a file with more complete data on diagnostic workup, medical and family history, and followup. It is hoped that at least half of the cancer patients diagnosed in the province will eventually be referred to the center providing an opportunity to get first hand information on many of the variables of interest for research.

The four record sources chosen for use in this study are of varying age and complexity. Death registration began early but is known to be incomplete until very recently. And the records are not detailed. Centralization of hospital data through insurance payment forms began 25 years ago; retrieval of detailed chart information was

made somewhat easier by using the hospital insurance diagnostic listing. Radiation oncology dates back 35 years and has reasonably good records on all referred patients. Cancer registration began in January, 1974 and covered only one year of the present study.

B. RECORD SURVEY

1. Review of Death Certificates

a. Objective

The objective of the review of death records was to compile, with the help of a Statistics Canada listing of all registered Hodgkin's deaths in the provinces, a list of all Newfoundland residents for which Hodgkin's disease was recorded as cause of death during the period 1965-74, together with other relevant data.

b. Methods

1) Statistics Canada Listing

Through the Vital Statistics Division of Statistics Canada, Ottawa, and with the permission of the Registrar of Vital Statistics, Newfoundland, a computer print-out was obtained listing all deaths in Newfoundland, 1965-74, in which the underlying cause of death was given as ICD code 201.0, Hodgkin's disease (see Figure 10 of the Appendix, p. A-12). Variables provided on this listing are given on p. 109.

year of death	district of residence
registration number	sex
coded cause of death	age at death

For analysis, the full name, exact residence, occupation, and birthplace were needed in addition. Hodgkin's deaths as given on the listing were ordered by year and by registration number and with the permission of the Registrar of Vital Statistics, the original certificates were consulted for the additional information required.

The one out-of-province death was in Ontario. With the permission of the Registrar for this province, the information was released and details related by telephone from Ottawa.

2. Followup of Other Files

For each patient in the hospital and radiation oncology files who had been "lost to followup", 11 patients in all, a search was made for a death certificate dated after the last clinical visit. In another 18 charts, mention had been made of the death of the patient; a search was also made for these certificates.

Certificates were not found for any of the patients in the "lost to followup" group. Certificates were found for 15 of the other patients; some deaths may have occurred outside the province. It had been hoped that a search could be made for Hodgkin's deaths in Ontario where

birthplace was given as Newfoundland on the certificate. However, in the process of obtaining information on the one known out-of-province death, it was learned that although it is requested, Ontario does not code birthplace for computer storage.

2. Review of Hospital Records

a. Objectives

The objective of the review of hospital records was to compile, with the help of a Department of Health print-out of all Hodgkin's admissions-separations, a list of all Newfoundlanders hospitalized with Hodgkin's disease during the period 1965-1974 together with other relevant data.

b. Methods

1) Admissions-Separations Listing

With the permission of the Hospital Insurance Division, a computer listing was provided by the Department of Health of all 1965 to 1974 hospital admissions with a primary or secondary diagnosis of Hodgkin's disease. (see Figures 11A and 11B of the Appendix, pp. A-13-14).

Individual patients had to be abstracted from the lists of yearly admissions by matching identifying variables; the complete list of variables on the listing is given below.

diagnostic code
diagnosis name
hospital code
chart number
admission number
separation date
physician numbers
hospital district
sex
MCP number
age
primary diagnosis
secondary diagnosis

The number and type of identifiers varied over the ten year period. From 1965 to 1969, only sex, age, hospital, and district of residence were available. In 1970 the hospital insurance number (MCP) was introduced and in 1971 the more general district of residence was replaced by the nine digit geographic code which specifically identifies communities. As mentioned previously, chart numbers were given voluntarily up to 1970 when each hospital was requested to submit this number on its admission-separation slips. Chart numbers for all hospitals were finally available in 1974.

Admissions-separations were sorted for each hospital for individual years. For the years 1971 to 1974 when age, sex, MCP number, admission number, and geographic code were available, duplications in admissions could be eliminated directly on the computer sheets by matching these variables. Prior to 1971, the district code, sex, and age were insufficient for matching. Consequently these early admissions were reordered by admission number and year and submitted to the appropriate hospital for identification

from admission registers. Chart numbers were then obtained from alphabetic surname files.

Records were not found for a total of 35 admissions. Twenty-five were matched to known patients on sufficient items to make identification highly probable. Examples of the matching process are given in Table 2 of the Appendix, p. A-16. Ten admissions were for persons with identifiers not matching any other patient; these were excluded. Five of these ten were admissions to hospitals outside Newfoundland and were coded by province only so that although an admission number was available, the hospital to which it belonged was not known. The admission-separation slips for out-of-province admissions up to 1975 had been destroyed. For some reason the slips for 1973 were saved. These were reviewed and followed up.

2. Patient Charts

It was decided to work initially in the St. John's region, that is with the four major hospitals within the city where the majority of lymphoma cases would be referred and where, because of the population concentration, the most cases were likely to occur.

When chart numbers had been obtained for all patients admitted during the 1965-1974 period, lists of requested charts were given to the records departments of the appropriate hospital. If a patient was admitted to several

hospitals, the chart of the larger, more centralized hospital was reviewed first. If the desired information was not available in this record, the hospital referring was contacted. In more cases than had been anticipated, early notes were available only in a small regional hospital or in a cottage hospital.

Details on the first admission for Hodgkin's disease were often difficult to find, particularly in hospitals using the serialized system where each admission was filed separately; most of the early charts which could not be located were filed under this system.

3. Review of Radiation Oncology REcords

a. Objective

The objective of the review of radiation oncology records was to compile a list of all Newfoundlanders with Hodgkin's disease who were being treated or being followed up during the period 1965-1974 together with other relevant data.

b. Methods

With the permission of the director of the Radiation Oncology Department of the General Hospital, cards filed under "haemic and lymphatic" were reviewed. All patients on file during the period 1965-1974 were noted. Some were on active treatment, some were on long term followup, and others were still listed but had been lost to followup.

corresponding charts were then pulled directly or requested from storage. Files for deceased or lost-to-followup patients which were stored at the former General Hospital were reviewed there.

Information on a number of variables was extracted. The variables are listed below.

year of diagnosis	date of admission
clinic number	age
pathology number	sex
referring hospital	occupation
name	first symptoms
residence	duration of symptoms
date of death	certified cause of death
clinical diagnosis	pathological diagnosis

4. Review of Tumor Registry Records

a. Objective

The objective of the review of tumor registry records was to compile a complete list of all Hodgkin's disease patients diagnosed during the year 1974 together with other relevant data.

b. Methods

With the permission of the medical director of the Provincial Tumor Registry, all cards filed under ICD code 201.0, were searched. Since official registration began in January, 1974, the format recommended by Statistics Canada has been used. The following variables were obtained from the abstract cards.

chart number
attending physician
MCP number
registry number
date of death
autopsy
notification by vital statistics
birthplace
date of birth
diagnostic code
method of diagnosis
certified cause of death

It is important to note that information was expected to be complete for only one year of this study, 1974, the first full year of the registry's operation.

Computer listings were provided for deaths and for hospital admissions. Preliminary reordering of these lists by registration number or chart number greatly simplified the subsequent search for death certificates and hospital records. Surveys of early hospital charts and of radiation oncology records required intermediate reviews of admission registers and abstract cards. In all instances, information from the original documents was recorded on worksheets, coded, and keypunched for further sorting and tabulation.

C. ANALYSIS OF DATA

1. Incidence and Mortality

a. Crude Rates

Population estimates were high for Newfoundland in 1966 and again in 1971; actual census figures for 1966 and 1971 were lower (see Table 3 of the Appendix, p. A-17. Consequently, although 1971 does not fall at the midpoint of the study period, it was decided to use that year's actual census figures for calculation of rates. All rates are presented as cases per 100,000 population.

Incidence is defined for this study as the number of new cases diagnosed per year. Crude annual rates for Canada and for Newfoundland are presented as incidence curves based on three year moving averages, each point representing the average of rates over three successive years and plotted on the middle year.

b. Adjusted Rates

The most recent incidence data for 1969-1974 for the provinces (updated in 1981) was provided by Statistics Canada. Although the organization, supporting legislation, and number of personnel vary from registry to registry within Canada, figures have been accepted as reported. The Newfoundland figures in the Statistics Canada material were adjusted to correspond to those derived from this study; a comparison of the published figures with figures from this

series showed minimal differences (see Table 16 of Results, p. 151). Deaths for each of the provinces were obtained from published data (Causes of Death, 1965-1974).

For **direct** adjustment of rates, the average annual rates for five year age groups of census divisions and provinces were applied to the appropriate age groups of the Canadian population. For **indirect** adjustment of incidence rates, the Canadian average annual rates, 1969-1974, for five year age groups (minus Ontario) were applied to the appropriate five year population groups of the provinces and of Newfoundland census divisions. Indirectly adjusted death rates were calculated similarly using average annual Canadian rates (1965-1974), including Ontario.

The results of direct and indirect age and sex adjustment were compared. Because there was little difference in the resulting rates (see Table 17 of Results, p. 154) and, because Canadian rates were more stable, indirect adjustment was preferred.

The results of rate adjustment are presented as Standard Incidence Ratios (SIR), Standard Mortality Ratios (SMR), and final adjusted rates (Bradford-Hill, 1977).

Adjusted rates were compared for significant differences in observed and expected numbers using the confidence limits for rare events based on the Poisson distribution (Bailar and Ederer, 1964).

It is important to note that all references to incidence for Canada as a whole exclude Ontario data.

2. Prevalence

Prevalence is defined for this study as the total number of cases living in the province or census division in a year. Rates were calculated for Newfoundland and for Newfoundland census divisions using figures from this series and the appropriate populations.

3. Stage and Histopathologic Type

The evaluation of the extent of disease, clinical staging, is essential for efficient treatment. The Ann Arbor system is widely used for staging Hodgkin's disease and was in use during the study period. A brief history of the development of staging and the criteria used in this system are given in Table 4 of the Appendix, p. A-18. Both the Jackson and Parker and the Rye histopathologic classifications were used during the period 1965-1974. The development of Hodgkin's classifications and a comparison of the two systems are given in Table 5 of the Appendix, p. A-19.

4. Survival

Survival rates were calculated by the actuarial method (Brown et al., 1981). Results are given as percentages of patients surviving at one, two, five, and 10 years by total group, by histological type, and by clinical stage.

For the one patient for whom an exact date of diagnosis was unobtainable, diagnosis was assumed for December of the year of his hospital admissions. Since he was lost to followup in this same year, his contribution to the table would have been one half year.

5. Geographic Comparisons

Crude and adjusted incidence and death rates were calculated for each of the ten Newfoundland census divisions (see map, Figure 12 of the Appendix, p. A-15). Death rates were calculated for the other nine provinces and incidence rates for the other eight provinces reporting to Statistics Canada. The adjusted rates were used for regional comparisons.

Place of birth was obtained where available in records. For the remainder of the patients for whom birthplace was not given, a search was made for a birth certificate using the birth date plus and minus five years. Data were not available to estimate the number of persons who would have been born in each census division over the last 90 years, the period over which the patient births ranged. Therefore, Newfoundland births from 1974-1980, the first to be categorized by census division, were averaged to provide expected values (Statistics Canada, unpublished tabulation, 1982). Births tabulated for 1922 and 1924 for Newfoundland were averaged by electoral district and compared with the

more recent data. (see Table 6 of the Appendix, p. A-20). Although the electoral districts for this period in no way match current census divisions, the general proportions for Labrador, the north, south, and west coasts, and for the Avalon Peninsula were similar. To give expected values greater than five, census divisions were grouped by region for comparisons of observed and expected proportions by the Chi-square goodness-of-fit test.

6. Risk Factors

a. Season of Onset of Disease

Date of diagnosis was equated to onset of disease (World Health Organization, 1978). If seasonal environmental factors have no relevance to disease onset, the times of diagnosis should be distributed evenly across the calendar year. No data were available for Newfoundland to try to account for seasonal variation in the use of primary care physicians. Dates of diagnosis were tallied by calendar quarter and compared with expected proportions using the Chi-square goodness-of-fit test.

b. Season of Birth

Assuming that no environmental factors acting at conception or birth influence the subsequent development of disease, patient births should be distributed across the calendar year in the same proportions as the whole of the Newfoundland population. Expected proportions of births

per calendar quarter were calculated from all Newfoundland births, 1967-1976, the earliest period for which data were available by month of birth (Statistics Canada, unpublished tabulation, 1967-1976). A second population was compiled from 1922 birth registration ledgers; the St. John's, St. Barbe (west coast) and Labrador regions were selected for this group. The 1967-1976 population did not differ significantly from the 1922 group when tested by Chi-square goodness-of-fit (see Table 7 of the Appendix, p. A-21). The proportions of patient births per calendar quarter were compared with expected proportions derived from the 1967-1976 population using the Chi-square goodness-of-fit test.

c. Occupation

Occupations were obtained wherever possible from patient records. They were categorized according to the occupational headings of the 1971 census (see Table 8 of the Appendix, p. A-22). Women giving "housewife" or "homemaker" as occupation and children under 15 years of age were excluded from this analysis as they are excluded in the census occupational data. The proportions of patient occupations were grouped generally by professional, skilled and unskilled categories and compared with proportions given for Newfoundland and for Canada (Statistics Canada, 1975), using the Chi-square goodness-of-fit test.

d. Urban Versus Rural Distribution

Urban and rural residence were compared by census divisions and provinces using 1971 census data (Statistics Canada, 1973). The definitions of urban and rural used by Statistics Canada are given in Table 9 of the Appendix, pp. A-23-24.

e. Sibship Size

Sibship size was given in some patient histories. It was assumed that this number of brothers and sisters would be a minimum number as most persons do not include deceased siblings unless specifically asked. Average sibship size was calculated for this group. For the remainder of the patients for whom no data was available, a sibship size of one was postulated. The average sibship size was then calculated for the total group of patients. For the group with known sibship size, frequencies were compared with those in previously published data (Gutensohn, 1982).

f. Other Socioeconomic Factors

Data on 18 characteristics of families, households, and housing collected during the 1971 census were selected for socioeconomic comparisons (Statistics Canada, 1973; 1975). Family size, multiple family households, and level of education were selected because of their postulated involvement in the etiology of Hodgkin's disease in the young.

Family income, house value, persons per room, water supply, household heating, and ownership of household appliances were added as additional indicators based on the field experience of the investigator. Definitions of variables are given in Table 9 of the Appendix, pp. A-23-24.

Three of the variables were subsequently eliminated because they were found not to be applicable over the whole of the study period, i.e., ownership of a television or automobile and use of wood or other fuel only. Television is still not available in all areas of the province, there are no roads connecting some communities, and wood is very scarce in some regions.

Association of incidence rates with these variables were evaluated using multiple regression analysis (Kim and Kohout, 1975).

D. COMPARISONS WITH INTERNATIONAL DATA

Comparisons of incidence and mortality data, and proportions of clinical stage and histologic type were made with previously published material. Sibship data were compared with data from Boston (Gutensohn, 1982), season of birth in this series was compared with the results of Fraumeni and Li (1969), and survivals were compared with Kaplan's data from Stanford (1980).

Other comparisons were made with material from five major surveys of cancer in general and Hodgkin's disease in particular. They are listed below:

1. Cancer Incidence in Five Continents, Volume III, 1976 (CIFC)
2. An International Survey of the Distribution of Lymphoreticular Tumours, International Union Against Cancer, 1971 (IUAC)
3. An International Symposium on Hodgkin's Disease, National Cancer Institute, 1972 (NCI)
4. New Primary Sites of Malignant Neoplasms in Canada, Statistics Canada, 1969-1974 (SC)
5. Third National Cancer Survey, U.S.A., National Cancer Institute, 1969-1971 (TNCS)

A more detailed description of these surveys is given in Tables 10 through 15 of the Appendix, pp. A-25-31. Sixteen countries or registries were selected for comparison from Cancer Incidence in Five Continents. Ibadan was chosen as the larger population of the two African countries given and Recife and Cali as representing urban and rural South American cities. Connecticut was included as the oldest registry in North America and representing a white population falling near the top of the socioeconomic scale. New Mexico is a rural and historically younger population. Bombay was included from the eastern countries along with Israel, a country with a mixture of ethnic groups and with good registry material. Miyagi is a rural

northern prefecture of Japan with a known higher incidence of Hodgkin's disease; Okayama is more industrialized and had a lower incidence. Germany and Norway were included from Europe, Norway in particular for its data on urban and rural incidence. Iceland, New Zealand, and Hawaii were small, island populations. Hawaii also provided a transplanted Japanese population. Birmingham, England represented an industrialized city and the southwest of England a rural area and the geographic origin of a large part of the Newfoundland population.

The IUAC study also included data from Ibadan, Recife, Cali, Israel, Japan, and Norway. The NCI symposium presented material from Uganda, Israel, Japan, and Connecticut.

Comparisons of death rates were between data from this series and rates published in World Health Statistics Report (1977) for a variety of countries. In addition to material from Ibadan, the United States, Israel, Japan, Iceland, Norway, and England and Wales, additional data from Mauritius, Mexico, Venezuela, Hong Kong, and the German Democratic Republic were included.

SECTION V: RESULTS

A. QUALITY OF AVAILABLE DATA

1. Death Certificates

a. List of Deaths

There were 46 deaths from Hodgkin's disease in Newfoundland from 1965 through 1974.

Initially forty-four deaths from Hodgkin's disease had been listed for Newfoundland by Statistics Canada; a further seven deaths that occurred during the study period, making an interim total of 51, were found in following up the 18 patients noted as dead in various records (see Table 16 of the Appendix, p. A-32). In one of these seven cases, Hodgkin's disease was given as a diagnosis secondary to Kaposi's sarcoma and therefore not coded. In the other six Hodgkin's disease did not appear on the certificate. In two, the cause of death was in error; subsequent checks in the hospital notes indicated confident histological confirmation of Hodgkin's disease. Four of the cases were excluded from the study because evidence for Hodgkin's disease prior to death had been weak (see Table 1, p. 127.)

Therefore, of the seven "Hodgkin's deaths" discovered during followup of other records, four were excluded and three were added to the final list of deaths making a total

of 47. One case which had been on the original list from Statistics Canada was also excluded when two pathology reports dated shortly before death were found; both confidently stated the diagnosis as anaplastic lung carcinoma.

Searches for the 11 patients lost to followup in other records produced no evidence of death in the intervening period (see Table 17 of the Appendix, p. A-33). Three of the 11 patients had moved out of the province. The remaining eight patients were assumed to be still alive.

TABLE 1

DEATH CERTIFICATES: RECORDS EXCLUDED FROM THE STUDY

A. From Statistics Canada listing of Newfoundland deaths

1. male, diagnosed in 1966 at the age of 19 as ? Hodgkin's disease or anaplastic carcinoma of lung with repeat biopsies inconclusive; died September, 1966 from "Hodgkin's disease"

B. From review of deaths on listing and found on followup

1. female, diagnosed in 1972 at the age of 66 as Hodgkin's disease, later as lymphosarcoma; died December, 1972 from "pulmonary edema due to lymphosarcoma"
2. male, diagnosed in 1970 at the age of 55 as ? Hodgkin's sarcoma of lung by needle biopsy; died January, 1970 from "respiratory failure due to cancer of the lung"
3. female, diagnosed in 1969 at the age of 46 as ? lymphoma, later as a secondary neoplasm; died April, 1970 from "carcinomatosis due to cancer of the cervix"
4. male, diagnosed in 1967 at the age of 49 as Hodgkin's disease, later epithelioma; died August, 1971 from "cachexia due to cancer of the right maxilla"

b. Registrations

A total of 44 deaths were listed for residents of the province by Statistics Canada, 43 of them occurring within the province. With the exclusion of the case later confirmed as anaplastic lung carcinoma (see Table 1, p. 127) and with the addition of the three records discovered in the followup searches, there was a total of 46 deaths due to Hodgkin's disease in the province between 1965 and 1974.

Forty deaths occurred in hospital (see Table 18 of the Appendix, p. A-34) and six at home. Sixty-five percent (26) of the deaths in hospital were at the major referral hospital. Excluding the one out-of-province death, the remaining 35 percent (14) were in two regional hospitals and six cottage hospitals. Forty-four of the death certificates were signed by a physician, one was signed by a public health nurse, and one was signed by a priest. Because of the unique registration system in Newfoundland, the interval between the death and its registration was also noted. Both the mean interval and the range of intervals was greater in the home deaths.

Seventeen variables were requested on the certificate. All were considered necessary either for matching or for later analyses except next of kin and details of the funeral and burial. Table 2, p. 129 summarizes the data missing from the certificates.

Birthplace was 76 percent complete; 54 percent of the certificates had occupation. Very few certificates had information on father's name, mother's name, or spouse's name in the case of married patients (range 9-22 percent).

TABLE 2

DEATH CERTIFICATES: SUMMARY OF MISSING INFORMATION n=46

Variable[1]	n complete	percent complete
Occupation	25	54
Birthplace	35	76
Name of father	5	11
Name of mother	4	9
Name of spouse[2]	7	22

[1]Sex, residence, date of death, place of death, date of registration were complete
[2]Total married = 32

2. Admission-Separation File and Hospital Records

a. Admission-Separation Listing

1) Summary of Listing

The annual number of admissions for Hodgkin's disease in the province was found to have doubled from 24 to 50 over the ten year period but the average number of admissions per patient, two, varied little from year to year (see Table 19 of the Appendix, p. A-35). Some patients were seen only once in a year and others as many as ten times. Generally, patients in the latter part of the decade had had more admissions per year. The number of

admissions outside the province had also increased although in most cases these were multiple admissions for the same patient.

There were 45 detectable omissions or errors in the computer listing. The gaps were missing MCP numbers or residence codes. The errors were wrong digits in MCP numbers or residence and hospital codes.

2) Geographic Distribution of Admissions

It was expected that the majority of patients would have been seen in St. John's and most records would be available there. However, the General Hospital, which houses the only radiotherapy center in the province, had inpatient records for only 57 percent of the patients; a much lower proportion than expected (see Table 20 of the Appendix, p. A-36). With the three other major hospitals in the city a total of 74 percent of patients was seen in St. John's. The remaining cases were inpatients only in regional and cottage hospitals or in institutions outside the province.

3) Distribution of Admissions Over the Course

With multiple admissions, the likelihood of finding all the information wanted for a patient increased. The pattern of admissions for individual patients varied over the study period (see Table 21 of the Appendix, p. A-37). Ninety-four percent of new cases in 1965-1969 were

hospitalized in the year of diagnosis compared to 79 percent of patients diagnosed from 1970-1974. And patients diagnosed in the latter part of the study were being admitted less frequently in the years subsequent to diagnosis. Of the total group, a quarter to a third of the patients were seen only once in the five to 10 years following diagnosis.

b. Chart Review

From the original list of 357 admissions for Hodgkin's disease, 347 were matched to 108 patients. Twelve cases were excluded; two were confirmed cases of Hodgkin's disease but were non-resident at the time of diagnosis; ten had been provisionally labelled Hodgkin's disease but were subsequently given other diagnoses (see Table 3, p. 132). Pathology reports were, unfortunately, missing from some of these charts but the notes of the attending physician indicated the pathologist's confidence in the reported histological diagnosis. Twelve cases were diagnosed prior to 1965 and were categorized as prevalent cases.

When chart numbers and/or names were obtained for all patients, the lists of consecutive chart numbers and corresponding names were used by the medical records staff at each hospital to pull charts for review. Twenty-seven variables were abstracted from patient charts and coded for analysis. A summary of the information missing is given in

TABLE 3

HOSPITAL CHARTS: RECORDS EXCLUDED FROM STUDY

A. Non-resident patients.
   1. male, a French seaman, diagnosed in 1973 at the age of 36 as Hodgkin's disease; returned to France
   2. male, a Polish fisherman, diagnosed in 1972 at the age of 42 as Hodgkin's disease; returned to Poland

B. Non-Hodgkin's patients.
   1. female, diagnosed in 1974 at the age of 11 as ? Hodgkin's disease; died in 1974, autopsy showed alveolar rhabdomyosarcoma
   2. female, diagnosed in 1973 at the age of 54 as ? Hodgkin's disease, biopsy later showed thyroid adenoma; alive and well in 1976 when lost to followup
   3. female, diagnosed in 1973 at the age of 4 as ? Hodgkin's disease, biopsy showed hyperplastic lymph node of neck; alive and well in February, 1982
   4. male, diagnosed in 1969 at the age of 62 as ? lymphosarcoma or ? Hodgkin's disease, with no resolution of diagnosis after repeat queries in 1975; died in April, 1978 from "cancer of the stomach"
   5. male, diagnosed in 1969 at the age of 55 as ? Hodgkin's sarcoma, later biopsies showed primitive lymphosarcomatous growth; died in January, 1970 from "cancer of the lung"
   6. male, diagnosed in 1968 at the age of 30 as lymphosarcoma and in 1972 as Hodgkin's disease with no report of conclusive biopsy; current status unknown
   7. female, diagnosed in 1967 at the age of 44 as cancer of the cervix and later, at age 46 as lymphoma with mediastinal obstruction with no followup biopsies; died in April, 1970 with "carcinomatosis from cancer of the cervix"
   8. male, diagnosed in 1966 at the age of 47 as probable Hodgkin's disease, later diagnosed as atypical anaplastic carcinoma with primary unknown; died in February, 1969
   9. male, diagnosed in 1966 at the age of 19 as ? Hodgkin's disease or anaplastic carcinoma of the lung with repeat biopsies inconclusive; died in September, 1966 from "Hodgkin's disease"
   10. female, diagnosed in 1965 at the age of 47 as ?Hodgkin's disease or ? malignant lymphoma of the mixed type, subsequent biopsy showed lymphosarcoma; died in November, 1970 from "septicemia from perforated bowel"

Table 4, below. Three patients had been treated outside the province and charts were not available for complete review. These patients were excluded from this table.

Date of birth, MCP number (after 1970), marital status, age at diagnosis, and date of diagnosis were usually given (range 89-96 percent complete). Less frequently mentioned were the method of diagnosis (83 percent), the pathology number (79 percent), and report of the confidence of the pathologist in his diagnosis (74 percent). Stage at diagnosis was least frequently given (38 percent).

TABLE 4

HOSPITAL CHARTS: SUMMARY OF MISSING INFORMATION n=81[1]

Variable[2]	n complete	percent complete
Date of birth	78	96
MCP (after 1970)	76	94
Marital status	75	93
Occupation	73	90
Date of diagnosis	72	89
Age at diagnosis	73	90
Method of diagnosis	67	83
Pathology number	64	79
Confidence in diagnosis	60	74
Stage	31	38

[1]Excluding three patients on whom not enough information was available.

[2]Sex and residence were complete on all charts.

3. Radiation Oncology Records

a) Abstract Cards

Ninety-nine abstract cards were found for Hodgkin's patients being followed by the radiation oncology department of the General Hospital. Eighty of these were patients diagnosed during the study period. Nineteen were patients diagnosed prior to 1965 and therefore categorized as prevalent patients.

b) Charts

Charts were requested for all patients. Of the 80 patients diagnosed between 1965 and 1974 three were found not to be Hodgkin's on the basis of subsequent notes and were excluded from the study (see Table 5, below).

TABLE 5

RADIATION ONCOLOGY RECORDS: RECORDS EXCLUDED FROM STUDY

1. male, diagnosed in 1972 at the age of 76 as Hodgkin's disease of the stomach; died in 1975 from "gastric adenocarcinoma"
2. male, diagnosed in 1969 at the age of 20 as atypical Hodgkin's disease; later pathology review showed atypical malignant sinus histiocytosis; died in 1978
3. male, diagnosed in 1968 at the age of 46 as ?Hodgkin's disease of the nasopharynx; died in May, 1969 with autopsy showing reticulum cell sarcoma of the nasopharynx

Thirty-seven of the remaining 77 patients had died as of April, 1982. Twenty-eight were known to be still alive in 1981. Twelve had been lost to followup, one in 1974 and the others between 1978 and 1980.

The charts of all patients were reviewed. Table 6, below summarizes the data missing from these records. Sex, residence, and method of diagnosis were given on all charts. Date of birth, MCP number (after 1970), marital status, date of diagnosis, and age at diagnosis were complete for most patients (range from 89-99 percent). Pathology report numbers were given for 85 percent of patients, occupation for 68 percent, and stage and type for 65 and 79 percent respectively, of cases.

TABLE 6

RADIATION ONCOLOGY RECORDS: SUMMARY OF MISSING INFORMATION
n = 77

Variable	n complete	percent complete
Date of birth	69	90
MCP (after 1970) n=46	44	96
Marital status	74	95
Occupation	53	68
Date of diagnosis	76	97
Age at diagnosis	77	99
Pathology report number	64	83
Stage	50	65
I-IV/A or B (n = 40)		
I-IV/ (n = 10)		
Type	61	79
Lukes (n = 22)		
Rye (n = 39)		

Final Status	
Alive	28 (36 percent)
Dead	37 (48 percent)
Lost to followup	12 (15 percent)

Sex, residence, and method of diagnosis complete on all charts

Of the 64 incident patients for whom a pathology report number was mentioned, only 62 mentioned the hospital where the biopsy examination was made. Sixty percent (37) of these biopsy specimens were examined in city hospitals, 32 percent in regional hospitals, six percent in cottage hospitals, and three percent in mainland hospitals. Four patients had had pathology reviewed elsewhere. In all cases, the local diagnosis was upheld.

Thirteen percent of the patients on the final list had been referred for treatment elsewhere. Notes indicated that seven patients had been treated at the Princess Margaret Hospital, Toronto; two had had treatment at the Royal Victoria Hospital, Montreal, and one patient had been seen at each of three hospitals, the Montreal Children's Hospital, the Hospital for Sick Children, Toronto, and Toronto Western Hospital.

4. Tumor Registry Records

Six Hodgkin's patients were registered as diagnosed in 1974. Information on the desired variables was either fully complete or non-existent (see Table 7, p. 137). Although space was provided for social insurance number and birthplace, these were never given. One of the six patients died within the year after diagnosis. Date of death and cause were given on his abstract card but the other death information requested was not given.

TABLE 7

TUMOR REGISTRY RECORDS: SUMMARY OF MISSING INFORMATION n=6

Variable[1]	n complete	percent complete
Social insurance number	0	
Death registration number[2]	0	
Cancer on certificate	0	
Autopsy	0	
Survival in months	0	

[1]Sex, date of birth, MCP number, residence, date of diagnosis, method of diagnosis, hospital, multiple primaries, date of death, and cause of death were complete in all records.

[2]Total deaths = 1.

5. Comparison of Records

Certain variables are considered of particular importance as identifiers for both the accuracy of an individual's record and for record linkage. With the overlapping of four data sets, notwithstanding the small numbers of tumor registry records and the relatively small number of death certificates, there were enough duplications of variables to have some check on accuracy.

Several charting systems use numbers incorporating either the MCP number or date of birth. Mismatches in either would lead to duplicate files. In addition, month and year of diagnosis and of death are used to compute survival rates. Errors in these, particularly in a large series, could bias results.

Of the 90 incident patients, approximately a third (35) had three records to compare. In most cases, these were a hospital record, a treatment record, and a death certificate. Half of the patients had two records (44), usually radiotherapy and hospital records. Eleven patients had only one record; these were split between hospital (5) and radiotherapy (6). This information is summarized in Table 8, below.

TABLE 8

COMPARISON OF RECORDS: NUMBER OF RECORDS PER PATIENT n=90

A. 3 records per patient		35
hospital/radiation oncology/death	31	
hospital/radiation oncology/registry	4	
B. 2 records per patient		44
hospital/radiation oncology	36	
hospital/death	6	
hospital/registry	2	
C. 1 record per patient		11
hospital	5	
radiation oncology	6	
D. Total patients		90

MCP numbers could be compared within an individual's records in 46 cases; the remainder of patients had only one record giving an MCP number or they were among those patients diagnosed and treated prior to the assignment of the MCP number. Of the 46 record sets, the insurance number

number did not match in seven of the cases indicating a clerical error rate of 15 percent (see Table 9, p. 140).

Date of birth could be compared for 60 patients; the remaining cases had only one record and in one case, the full date of birth was missing. In 13 cases dates of birth did not match indicating a clerical error rate of 21 percent.

Date of diagnosis as given in hospital discharge summaries, radiotherapy progress notes, and pathology reports, was available for comparison in 58 cases; 27 patients had only one record with this date and in the records of five patients, no mention was made of date of diagnosis. Most of the errors were trivial; in 27 of the 28 mismatched dates, the difference was less than one month; in one case, the difference exceeded one month.

Comparison of dates of death was possible in 38 cases; in six patients only one record was available and for 46 patients presumed to be alive, there would be no death record. There was only one case in which the dates did not match (3 percent) and this was for month only; years of death matched in all cases.

Because various files used in medical research employ either MCP number or date of birth as a key identifier, matching the date of birth and MCP number seemed a priority for record linkage. In 73 patients, sufficient records were available for comparison. About half of the patients

TABLE 9

COMPARISON OF RECORDS: IDENTIFYING VARIABLES n=90

	MCP[1]	DOB[2]	DOD	DODX
A. Number of patients excluded from matching	44	30	52	32
Variable on only one record	27	30	6	27
Variable on none of patient's records	17	0	46	5
B. Number of patients with sufficient records for matching	46	60	38	58
Variable appeared on two records	43	56	20	55
Variable appeared on three records	3	4	18	3
C. Number of records which did not match	7	13	1	27
Percent of records which did not match	15	22	3	47

D. Comparison of date of birth with MCP

Number of records excluded from matching =	17	
Number of patients with records for matching =	73	
Number not matched =	22	(30 percent)
Minor mismatch[3] =	6	(8 percent)
Major mismatch =	14	(19 percent)
Consistent[4] =	10	(14 percent)
Inconsistent =	4	(5 percent)

[1]MCP=medical insurance number; DOB=date of birth; DOD=date of death; DODX=date of diagnosis

[2]36 percent with one month difference (21), 8 percent with more than month's difference (5), and 2 percent with more than one year's difference (1)

[3]Patient records could be linked if more than two records were available for either date of birth or MCP

[4]All dates of birth and all MCPs were consistent but MCP did not match date of birth

(42) had two recorded dates of birth to compare with two recorded MCP numbers. Another 14 had only one each for comparison.

In 22 patients (30 percent), the MCP number did not match date of birth in at least one comparison. As this was a serious error rate, the types of mismatches were looked at in more detail. In six of the 22 cases, it was possible to detect the 'wrong' entry since there were three pieces of data, i.e., two MCP numbers and one date of birth or two dates of birth and one MCP number with one pair in each three items matching exactly. However, in 14 of the 22, using all the data available, it was still not possible to match MCP number with date of birth. In the majority of these (71 percent) there was consistency over several entries of either the MCP number or the date of birth or both so that the simplest explanation is that the MCP number was incorrectly assigned.

In summary, in 30 percent of cases there were errors. In 14 percent the error was presumed to be the wrong assignment of the MCP number; the remainder were clerical errors. In 19 percent of all cases there would have been no way to use date of birth and the MCP number to link records.

B. FINAL LIST OF PATIENTS

1. Merging Data Sets

The final list of patients comprises 90 incident patients, 15 prevalent patients diagnosed prior to 1965, and 46 deaths. From the multiple sources of data used in this study, 256 records in four data files were located (see Table 10, p.143). With the addition of death records found in followup and the exclusion of non-resident Hodgkin's patients, non-Hodgkin's cases, and cases diagnosed prior to 1965, 213 records remained representing 46 deaths and 167 records for incident patients diagnosed in the years 1965 through 1974. The excluded non-Hodgkin's cases were mostly patients with a provisional diagnosis of Hodgkin's who were subsequently found to have another tumor or a non-malignant condition, or they were patients whose records were so incomplete that they could not be moved even from the uncertain to probable category.

Had the study been based on only one of the two larger files, i.e., the hospital or the radiotherapy file, cases would have been missed; six cases were missing in the hospital file and 13 in the radiation oncology file (see Table 11, p.144). Two of the patients missed in the hospital group were diagnosed under the age of 15 and all treatment had been given as outpatients. Of the 13 patients who would have been missed had only the radiation

TABLE 10

FINAL LIST OF PATIENTS: MERGING OF RECORDS

Record	n	Non-Resident	Excluded	Added	Prevalence[1]	Incidence	Deaths
Death certificates	43	-	1	3	-	-	46
Hospital charts	108	2	10	-	12	84	-
Radiation oncology charts	99	-	3	-	19	77	-
Tumor registry records	6	-	-	-	-	6	-
Total records	256	2	14	3	31	167	46
Total patients					15	90	46

[1] Patients diagnosed prior to 1965

oncology file been searched, three patients were diagnosed and treated outside the province and three had died within the year of diagnosis.

TABLE 11

FINAL LIST OF PATIENTS: PATIENTS MISSED IN SINGLE RECORD SETS n=90

Record	n missed	percent missed
Death certificates	44	49
Hospital records	6	7
Radiation oncology records	16	18
Tumor registry records	0	0

2. FINAL LIST

a. Incident Patients

The criteria used for designating cases are listed in Table 12, p. 145. Definite cases had unequivocal pathology reports. Probable cases had either a clinical or radiological diagnosis and no pathology or a pathology report in which the histological appearance of the specimen was termed to be "consistent" with a diagnosis of Hodgkin's disease.

There were 90 incident patients on the final list of patients (see Tables 22A and B of the Appendix, pp. A-38-43). Eighty were considered firm diagnoses; 10 were labelled probable. In the probable category were patients who had died before definitive diagnostic tests could be completed, one clinically diagnosed patient with negative

TABLE 12

FINAL LIST OF PATIENTS: CRITERIA FOR DESIGNATION AS A CASE

A. Incident cases; n=90

1. Certain cases; n=80
   a. The presenting symptoms and signs were consistent with those of Hodgkin's disease.
   b. There was a confident statement of diagnosis by the pathologist or review panel.
   c. All records subsequent to diagnosis were consistently coded as Hodgkin's disease.

2. Probable cases; n=10
   a. The pathology report of biopsy or the majority opinion of a review panel stated that the tissue appearance was consistent with Hodgkin's disease; clinical examination and response to therapy were supportive of the diagnosis but Sternberg-Reed cells were not seen.
   b. Alternatively, the diagnosis was made on a radiological finding of mediastinal mass and subsequent response to therapy plus the appropriateness of presenting symptoms and signs.
   c. Alternatively, the diagnosis was made on clinical findings and on subsequent response to therapy but biopsy findings were repeatedly negative.
   d. Alternatively, repeated visits to an out-of-province hospital were coded to Hodgkin's disease and no information was available to recommend exclusion as a case.

B. Prevalent cases (diagnosed prior to 1965); n=15

The pathologist's confirmation of diagnosis was available in a formal report or discharge summary and subsequent hospital admissions or therapy records or a death certificate was coded to Hodgkin's disease.

C. Deaths; n=46

1. The death certificate stated that death was due to Hodgkin's disease and a pathology report or discharge summary was found with the pathologist's confirmation of diagnosis.
2. All criteria for an incident case were met with the death certificate being found on followup.

biopsies but who had responded to radiotherapy, and one patient who had had multiple admissions to an out-of-province hospital coded to Hodgkin's disease. Details of the latter case are unknown. The hospital involved was willing to provide the information requested but the one chart number available on insurance forms produced the chart of a patient not of the same sex, age, or residence.

Two measures of data quality in the cancer field are the proportion of cases confirmed by pathology and the proportion of cases discovered only by notification of death.

The proportion of histologically confirmed cases of Hodgkin's disease ranged from 94 to 97 percent in Canada (1970-1974) and from 80 to 100 percent in Newfoundland (1965-1974). See Table 13, p. 147. The proportion of all neoplasms confirmed by histology remained fairly constant in Canada but had increased in Newfoundland from a low of 68.8 percent in 1970 to a high of 92.3 percent in males in 1974.

In this series of Hodgkin's disease patients, three cases, all male, were discovered only by death certificate (see Table 14, p. 148). One was diagnosed at autopsy, one survived only a month from diagnosis, and the remaining patient died three months after diagnosis. The proportions of cases first discovered by death certificate ranged from

TABLE 13

FINAL LIST OF PATIENTS: PROPORTIONS OF CASES HISTOLOGICALLY CONFIRMED[1]

	Year	Hodgkin's Disease Male	Hodgkin's Disease Female	All Sites Male	All Sites Female
Canada n = 2009					
	1970	95.1	95.5	86.3	90.0
	1971	96.7	97.1	88.0	90.6
	1972	95.4	96.6	85.9	89.5
	1973	93.8	94.0	87.1	90.0
	1974	94.4	94.6	88.2	91.4
Newfoundland n = 90					
	1965	80.0	100.0	NA	NA
	1966	100.0	100.0	NA	NA
	1967	100.0	100.0	NA	NA
	1968	100.0	100.0	NA	NA
	1969	100.0	100.0	NA	NA
	1970	90.0	100.0	68.8	76.4
	1971	100.0	100.0	77.2	79.3
	1972	100.0	100.0	77.4	82.2
	1973	100.0	100.0	87.1	89.3
	1974	100.0	100.0	92.3	93.7

[1]Statistics Canada, 1970-1974 plus this series.

4.9 to 8.1 percent in Canadian males 1969-74) and from 0 to 25 percent in this series. The percentage for all sites had dropped slightly from 15.1 to 12.9 percent; the proportion in Newfoundland had dropped dramatically in males from 26.5 percent in 1970 to 4.9 percent in 1974. The provincial tumor registry began operation in 1974 and during its first year went back to collect cases from 1973. The decrease in death certificate registration for all sites

TABLE 14

FINAL LIST OF PATIENTS: PROPORTIONS OF CASES DISCOVERED BY DEATH CERTIFICATE[1]

	Year	Hodgkin's Disease Male	Hodgkin's Disease Female	All Sites Male	All Sites Female
Canada n = 2009					
	1970	8.1	8.0	15.1	12.1
	1971	4.9	2.9	14.0	11.6
	1972	8.4	6.6	15.0	12.1
	1973	5.6	8.6	13.1	11.0
	1974	6.9	8.4	12.9	10.7
Newfoundland n = 90					
	1965	-	-	NA	NA
	1966	16.7	-	NA	NA
	1967	25.0	-	NA	NA
	1968	-	-	NA	NA
	1969	16.7	-	NA	NA
	1970	-	-	26.5	20.9
	1971	-	-	22.5	20.9
	1972	-	-	21.0	17.2
	1973	-	-	14.8	12.8
	1974	-	-	4.9	5.3

[1]Statistics Canada, 1970-1974 plus this series.

would be at least partly due to this first year of active registration of cancer cases.

b. Prevalent Cases

Prevalent cases diagnosed prior to 1965 were noted during the records review. Initially, 19 patients were discovered in hospital and radiation oncology records. One was later found not to be Hodgkin's and three had been lost to followup before 1965 although their records were still carried by radiation oncology. Of the final 15 prevalent

patients (see Table 23 of the Appendix, p. A-44), 11 died during the study period, one died in 1975, and another in 1977. One was lost to followup in 1979 and one was alive and well in December, 1981.

c. Deaths

As was mentioned in the preceding section of the results of this study, Statistics Canada listed 44 Hodgkin's deaths for Newfoundland for the period 1965-1974. One record was excluded and three deaths were added in following up incident and prevalent patients for a total of 46 patients (see Table 24 of the Appendix, pp. A-45-46).

The summary of patient records is given in Table 15, below.

TABLE 15

FINAL LIST OF PATIENTS: SUMMARY OF RECORDS

Category	male	female
A. Incident cases	60	30
Certain	53	27
Probable	7	3
B. Prevalent cases	8	7
C. Deaths	33	14

C. EPIDEMIOLOGY

1. Incidence

a. Annual Crude Incidence Rates

Rates are shown both for certain cases alone and for certain and probable cases together in Table 16, p. 151. All subsequent calculations and presentations have used 90 cases as the total incident patient group.

In the same table, crude rates for Newfoundland calculated from this series are compared with figures published for Newfoundland by Statistics Canada. There is little difference in yearly or summary rates. Rates for this series were 2.7 and 1.4 per 100,000 for males and females, respectively, for 1969-1974; rates of 2.5 and 1.5 were published for Newfoundland by Statistics Canada. Crude rates for Newfoundland and for Canada (1969-1974) have been compared as moving averages in incidence curves in Figure 1, p. 152. Each point represents the average of the rates of three successive years (the point plotted for 1966 is the average of the rates for 1965, 1966, and 1967). Incidence in both sexes was higher in Canada in all years. From 1971 to 1973 there was an increase in Hodgkin's disease in Canadian males and a decrease in incidence in Newfoundland males.

TABLE 16

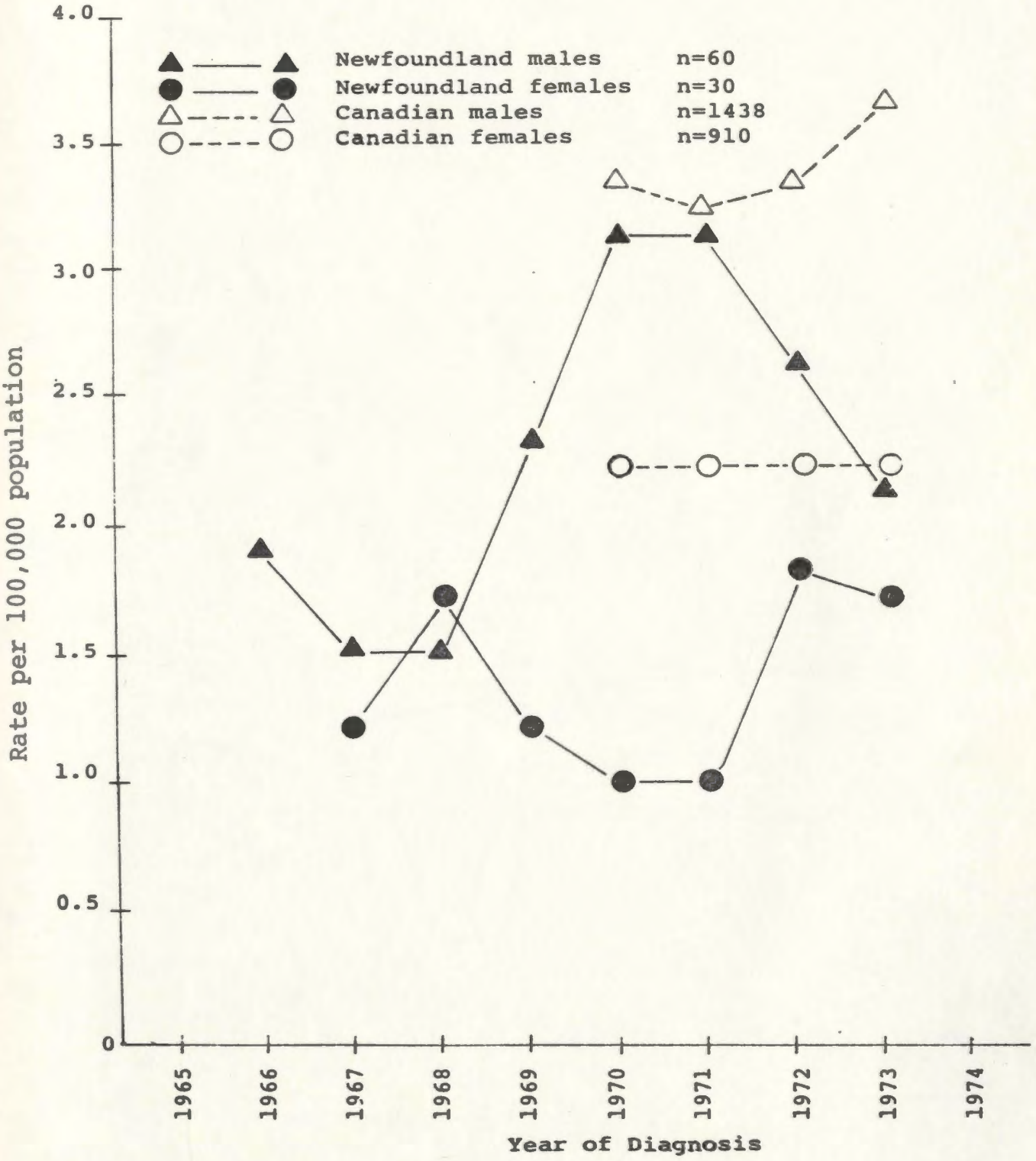
INCIDENCE: CRUDE RATES, NEWFOUNDLAND, 1965-1974 n = 90

Year	Sex	Statistics Canada [1]		This series			
				Certain		Certain + Probable	
		n	rate	n	rate	n	rate
1965	M [2]	NA		4	1.5	5	1.9
	F			0		0	
1966	M	NA		5	1.9	6	2.3
	F			0		0	
1967	M	NA		4	1.5	4	1.5
	F			6	2.3	6	2.3
1968	M	NA		2	0.8	2	0.8
	F			3	1.2	3	1.2
1969	M	4	1.5	6	2.3	6	2.3
	F	5	2.0	4	1.6	4	1.6
1970	M	9	3.4	8	3.0	10	3.8
	F	2	0.8	1	0.4	2	0.8
1971	M	8	3.0	8	3.0	9	3.4
	F	2	0.8	2	0.8	2	0.8
1972	M	5	1.9	5	1.9	6	2.3
	F	4	1.6	4	1.6	4	1.6
1973	M	8	3.0	6	2.3	6	2.3
	F	8	3.1	6	2.3	8	3.1
1974	M	6	2.3	5	1.9	6	2.3
	F	2	0.8	1	0.4	1	0.4
1965-1974	M	NA		53	1.9	60	2.3
	F			27	1.1	30	1.2
1969-1974	M	40	2.5	38	2.4	43	2.7
	F	23	1.5	18	1.2	21	1.4

[1] Data available from Statistics Canada only from 1969
[2] Year of diagnosis not obtainable for one male patient

FIGURE 1

INCIDENCE: CRUDE RATES, THREE YEAR MOVING AVERAGES, CANADA, 1969-74, NEWFOUNDLAND, 1965-74


Newfoundland males n=60
Newfoundland females n=30
Canadian males n=1438
Canadian females n=910
Rate per 100,000 population
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
Year of Diagnosis

b. Comparisons of Adjusted Incidence Rates

Crude rates for the provinces were adjusted both directly and indirectly as described in Section IV, p.117. A comparison of these rates in Table 17, p. 154 shows that there is little difference in the results of the two methods. Newfoundland's directly adjusted rates for 1969-74 were 3.0 and 1.4 per 100,000 for males and females respectively. With indirect adjustment the rates were 3.0 and 1.5. Directly and indirectly adjusted rates for 1965-74 were 2.5 and 1.3 compared to 2.4 and 1.1. Indirect adjustment was used for all subsequent standardizations.

Adjusted incidence rates and Standard Incidence Ratios (SIRs) are shown for Newfoundland census divisions in Figure 2, p. 155. The raw data and the crude annual rates from which they were calculated are given in Table 25 of the Appendix, p. A-47. The rate for Division 9 males at 5.9 per 100,000 (SIR 200) was considerably higher than for Newfoundland males (1965-74), 2.5 (SIR 73) but the number of cases did not significantly exceed expectation. There were fewer male patients than expected in Divisions 2 and 7 (SIRs 25 and 43) and fewer female cases than expected in Divisions 4, 5, 7, 8, and 10 where SIRs ranged from 25 to 50. Division 3 had no female cases during the study period. Sixty percent of the census divisions had half or fewer of the cases predicted by Canadian rates. Division 7, which includes Bonavista and Trinity Bays was below

TABLE 17

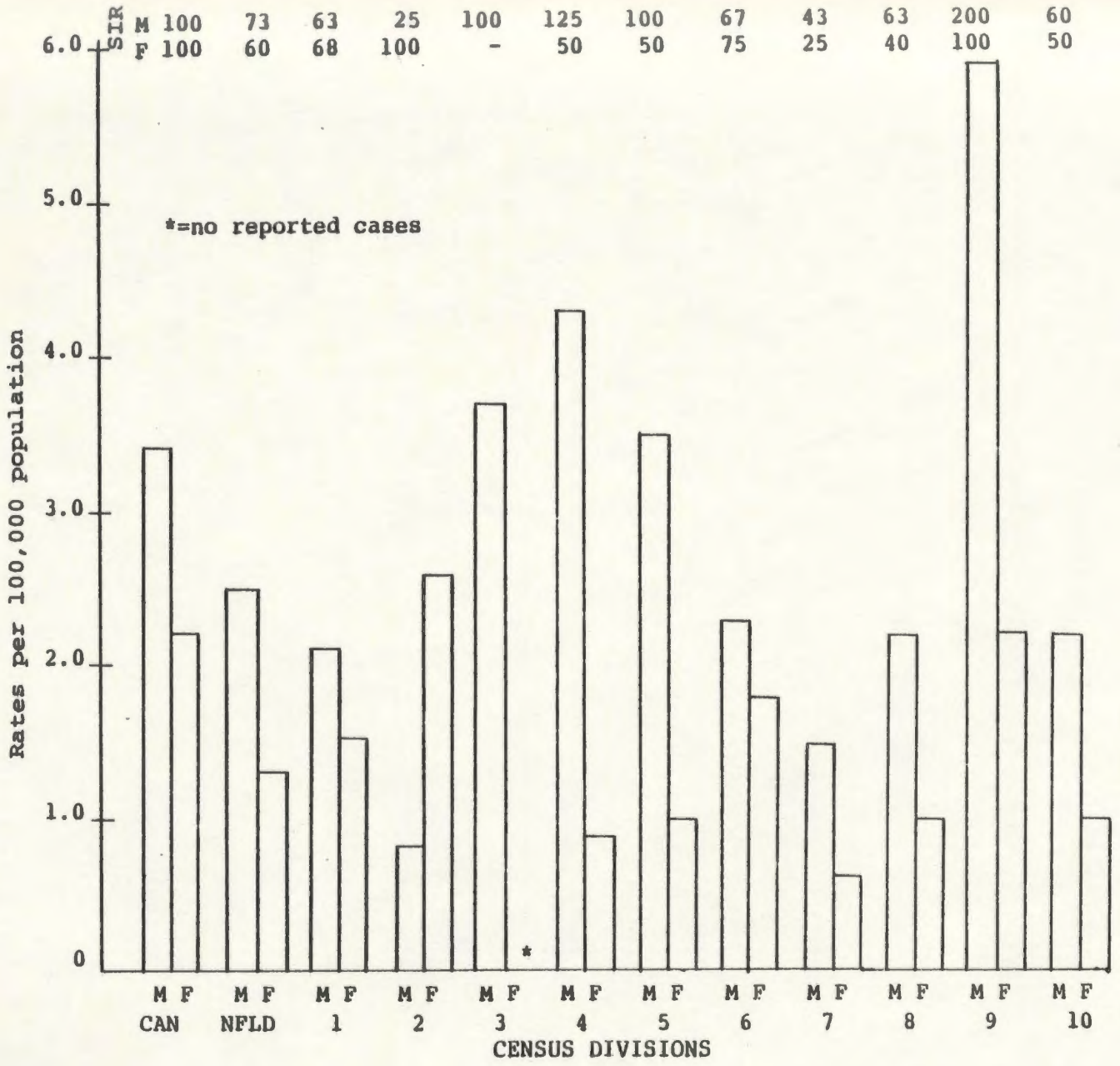
INCIDENCE: AVERAGE ANNUAL DIRECTLY AND INDIRECTLY ADJUSTED RATES, 1969-1974 [1] n=90

Region	Sex	Crude Rate	Directly Adjusted Rate	Indirectly Adjusted Rate
CANADA	M	3.4		
	F	2.2		
Newfoundland	M	2.7	3.0	3.0
	F	1.4	1.4	1.5
P.E.I.	M	2.3	2.5	2.3
	F	0.9	0.9	0.9
Nova Scotia	M	3.1	3.0	3.0
	F	1.2	1.8	1.9
New Brunswick	M	3.5	3.6	3.5
	F	1.4	1.4	1.4
Quebec	M	3.4	3.4	3.4
	F	2.1	2.1	2.1
Manitoba	M	3.5	3.4	3.3
	F	2.6	2.5	2.5
Saskatchewan	M	3.9	3.8	3.8
	F	2.0	2.0	2.1
Alberta	M	3.3	3.4	3.3
	F	2.6	2.6	2.7
B.C.	M	3.9	3.6	3.3
	F	2.7	2.6	2.6

[1] indirectly and directly adjusted rates for Newfoundland, 1965-1974 were 2.5 and 1.3; 2.4 and 1.1, respectively

FIGURE 2

INCIDENCE: AVERAGE ANNUAL ADJUSTED RATES AND SIRS, CANADA AND NEWFOUNDLAND CENSUS DIVISIONS, 1965-74


SIR
M 100 73 63 25 100 125 100 67 43 63 200 60
F 100 60 68 100 - 50 50 75 25 40 100 50
6.0
5.0
4.0
3.0
2.0
1.0
0
*=no reported cases
Rates per 100,000 population
M F M F M F M F M F M F M F M F M F M F M F M F
CAN NFLD 1 2 3 4 5 6 7 8 9 10
CENSUS DIVISIONS

expected numbers in both sexes (SIRs 43 in males and 25 in females). There seems to be no particular pattern; Division 9 stands out as a high incidence area. There were few male cases on the east coast of the island and few female cases in the western and central divisions. However, numbers are very small.

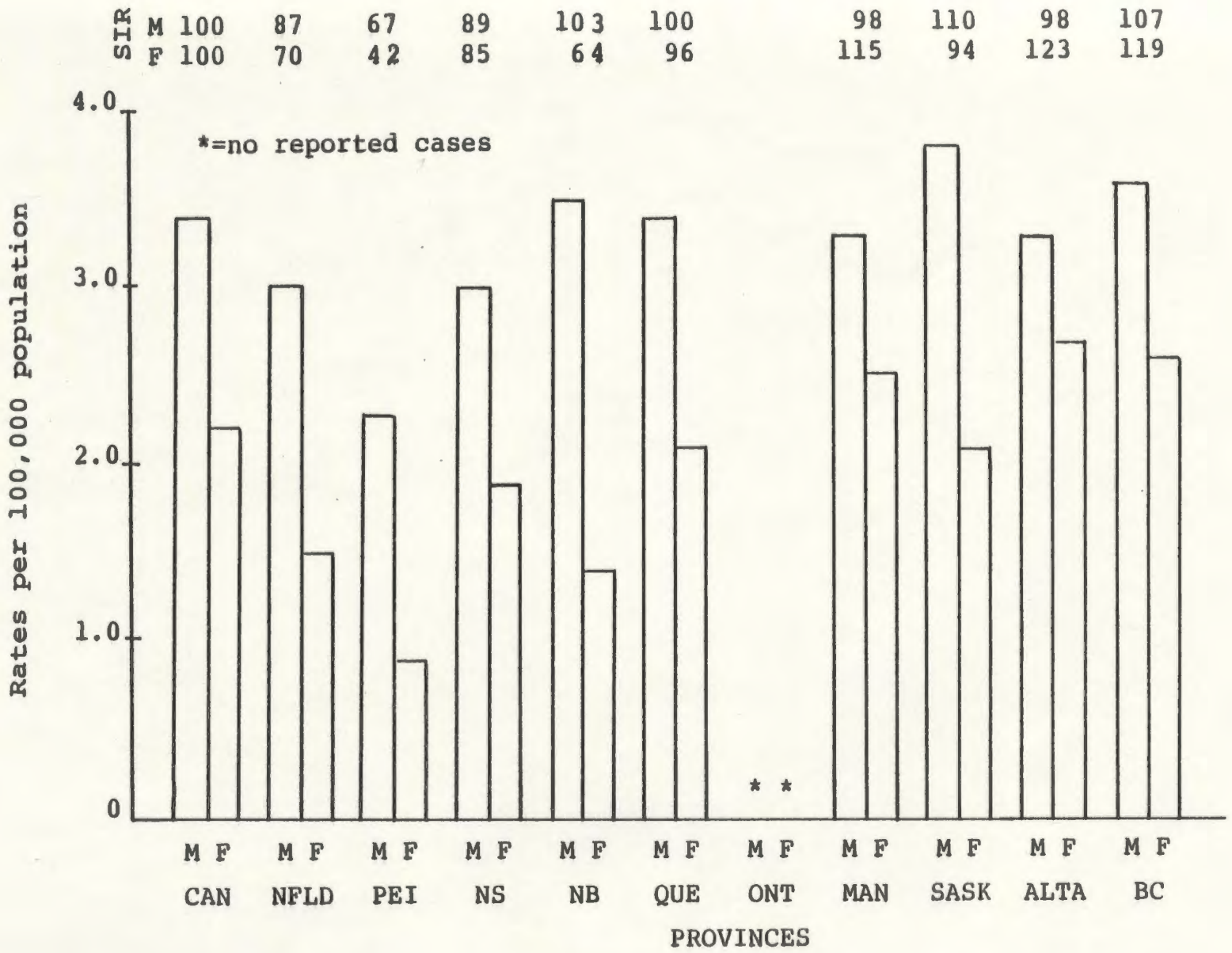
Adjusted rates and SIRs for Newfoundland and the other provinces for 1969 to 1974 are shown in Figure 3, p. 157. Annual crude and adjusted rates are shown in Tables 26 and 27 of the Appendix, pp. A-48-49. Newfoundland rates for males and females were 87 and 70 percent of those of Canada. Prince Edward Island had the lowest SIRs at 67 and 42 for males and females respectively, with Newfoundland second, followed by Nova Scotia (SIRs 89 and 85) and New Brunswick (SIRs 103 and 64). The SIRs for females in Prince Edward Island and New Brunswick fell outside 95 percent confidence limits (Bailar and Ederer,1964). The highest ratios were in the western provinces where SIRs ranged from 98 to 110 in males. There were 10 percent more cases in Saskatchewan males and 19 percent more female patients in British Columbia than expected from Canadian rates. The SIRs for females in Alberta and British Columbia were significantly higher than expected.

c. Age-specific Rates

Age-specific rates for five year age groups for Newfoundland and the other provinces are shown in Table

FIGURE 3

INCIDENCE: AVERAGE ANNUAL ADJUSTED RATES AND SIRS, CANADA AND PROVINCES, 1969-74


SIR
M 100 87 67 89 103 100 98 110 98 107
F 100 70 42 85 64 96 115 94 123 119
4.0
3.0
2.0
1.0
0
*=no reported cases
Rates per 100,000 population
M F M F M F M F M F M F M F M F M F M F
CAN NFLD PEI NS NB QUE ONT MAN SASK ALTA BC
PROVINCES

28 of the Appendix, p. A-50. These have been plotted in Figure 4, pp. 159-160. The classic bimodal curve is apparent in data for Canada as a whole. All provinces have a well-defined peak in young adults; the older peak is less marked in the smaller provinces. Age-specific rates in the youngest age groups were generally higher in this and the other Atlantic provinces.

d. Sex Ratios

Sex ratios for the total study group, for age groups, for stages, and for histopathologic types are given in Table 18, p. 161. A ratio of two male patients to one female patient was found in most categories, with ratios ranging from 0.7:1 in the Jackson and Parker para-granuloma group to 3.5:1 in older patients. Overall, higher ratios were seen in older age groups, in more advanced stages, and in cases with poorer prognosis. The sex ratios were also higher in the unstaged and untyped groups.

e. Stage and Histopathologic Type at Diagnosis

The proportions of clinical stage and histological type at diagnosis are shown by age in Figure 5, p. 162 and Tables 29 and 30 of the Appendix, pp. A-51-52. Stage at diagnosis was available for 64 of the 90 patients. As expected Stages I and II were seen primarily in the young and the young adults. The more advanced stages were found in all age groups.

FIGURE 4

INCIDENCE: AVERAGE ANNUAL AGE-SPECIFIC RATES, CANADA AND PROVINCES, 1969-74

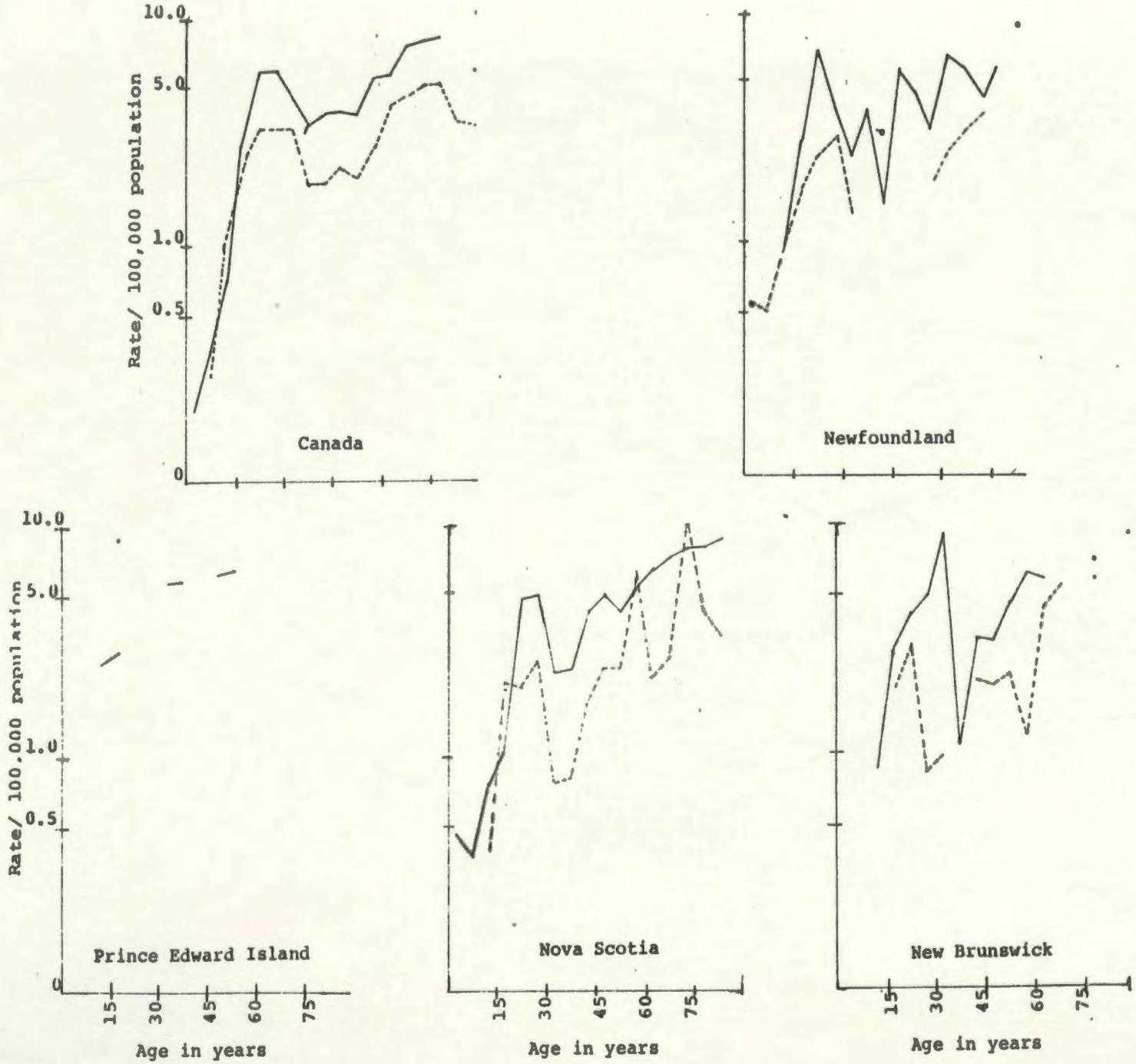

10.0
5.0
1.0
0.5
0
Rate/ 100,000 population
Canada
Newfoundland
Prince Edward Island
Nova Scotia
New Brunswick
15
30
45
60
75
Age in years

FIGURE 4 (CONTINUED)

INCIDENCE: AVERAGE ANNUAL AGE-SPECIFIC RATES, CANADA AND PROVINCES, 1969-74

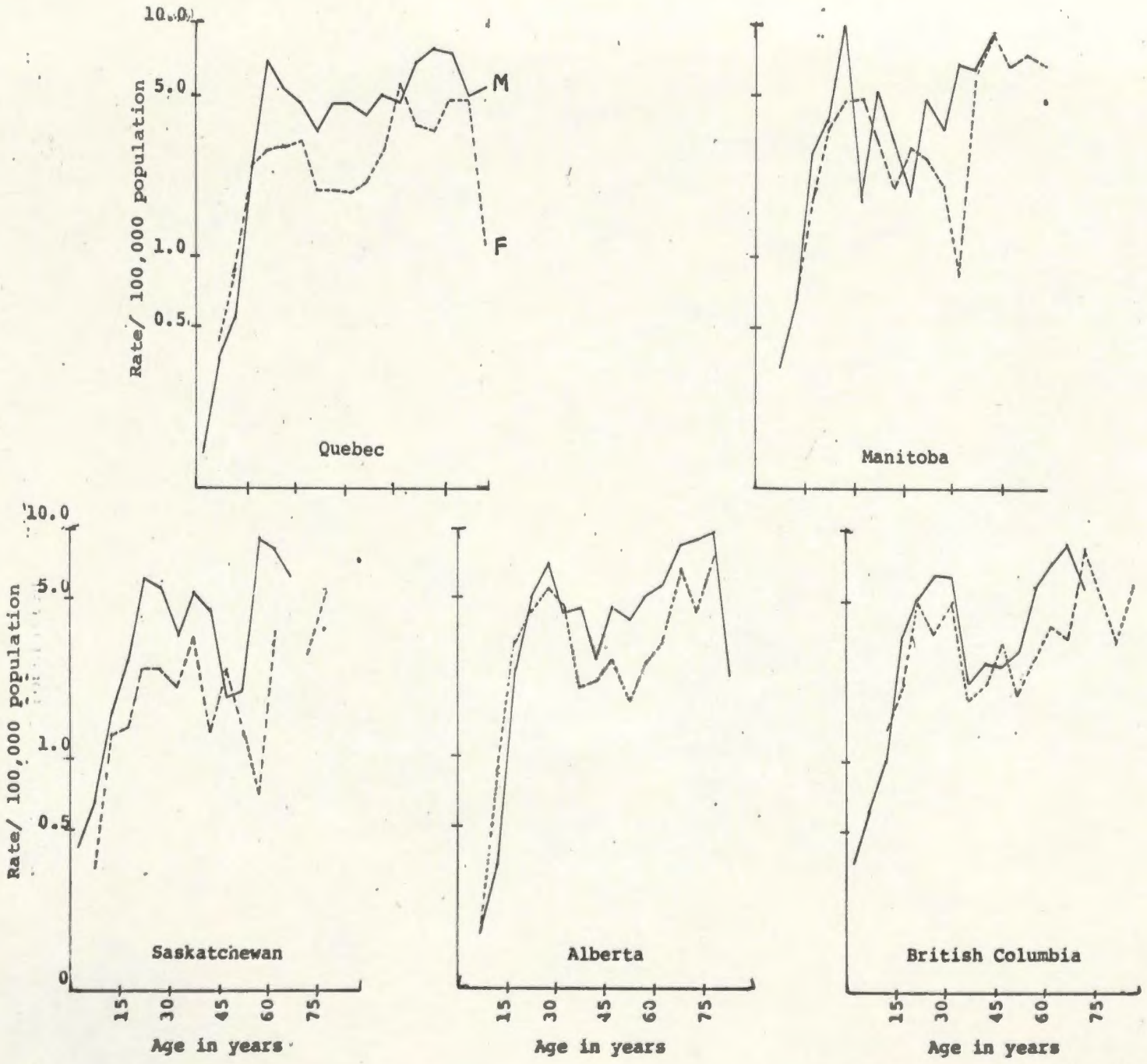

10.0
5.0
1.0
0.5
0
Rate/ 100,000 population
M
F
Quebec
Manitoba
Saskatchewan
Alberta
British Columbia
15
30
45
60
75
Age in years

TABLE 18

INCIDENCE: SEX RATIOS n = 90

Category	Number M	Number F	Ratio
A. Total study group	60	30	2:1
B. Age groups			
0-14	10	4	2.5:1
15-24	16	11	1.5:1
25-34	9	4	2.3:1
35-44	5	4	1.3:1
45-54	7	2	3.5:1
55-64	7	2	3.5:1
65-74	5	2	2.5:1
75+	1	1	1:1
C. Stage at diagnosis			
Stage IA	7	6	1.2:1
Stage IIA/B	15	12	1.3:1
Stage IIIA/B	11	4	2.8:1
Stage IVA/B	6	3	2:1
Unstaged	21	5	4.2:1
D. Histopathologic type			
Jackson and Parker			
granuloma	6	3	2:1
paragranuloma	2	3	0.7:1
sarcoma	5	0	
Rye			
lymphocyte predominant	2	1	2:1
nodular sclerosing	14	8	1.8:1
mixed cellularity	16	10	1.6:1
lymphocyte depletion	3	1	3:1
Untyped	10	6	1.7:1

FIGURE 5

CLINICAL STAGE AND HISTOPATHOLOGIC TYPE AT DIAGNOSIS


n=16
n=5
n=9
n=5
Untyped
Paragranuloma
Granuloma
Sarcoma
JACKSON AND PARKER TYPING n=19
n=3
n=22
n=26
n=4
Lymphocyte Predominant
Nodular Sclerosis
Mixed Cellularity
Lymphocyte Depletion
RYE TYPING n=55
n=26
n=13
n=19
n=8
Unstaged
Stage IA
Stage IIA
Stage IIB
n=6
n=9
n=2
n=7
Stage IIIA
Stage IIIB
Stage IVA
Stage IVB
ANN ARBOR STAGING n=64
0-14
15-29
30-44
45-59
60+
AGE GROUPS

Histological type was recorded for 74 of the 90 patients. Nineteen had been typed by Jackson and Parker criteria and 55 by the Rye classification. Of those patients typed by the earlier method, most were Hodgkin's granuloma (47 percent). The prognostically favorable paragranuloma was seen in the youngest and oldest groups. Hodgkin's sarcoma was not seen in young children. Nodular sclerosing disease and mixed cellularity were the commonest forms of disease in the group typed by the Rye classification (40 and 47 percent). Lymphocyte predominant and nodular sclerosing disease were seen in the young and young adults. The types with poorer prognosis, i.e., mixed cellularity and lymphocyte depletion, were seen across all age groups.

2. Prevalence

During the record reviews, prevalent patients were found who had been diagnosed prior to 1965 and who were under treatment during the study period. Rates were calculated using these patients plus the incidence patients who had been diagnosed from 1965-1974. Annual prevalence and prevalence rates for the province and for census divisions are given in Table 19, p. 164. The prevalence rate for the province had increased from 3.8 per 100,000 in 1965 to 11.7 per 100,000 in 1974. As expected from incidence figures, Division 9 showed high prevalence throughout the decade, ranging from 8.6 to 17.3.

TABLE 19

PREVALENCE: NEWFOUNDLAND AND CENSUS DIVISIONS, 1965-1974

Year	Newfoundland		1		2		3		4	
	n	rate	n	rate	n	rate	n	rate	n	rate
1965	20	3.8	11	5.1	1	3.7	-	-	-	-
1966	21	4.0	10	4.7	1	3.7	-	-	1	3.5
1967	25	4.8	14	6.5	-	-	-	-	2	7.1
1968	24	4.6	13	6.1	1	3.7	-	-	-	-
1969	33	6.3	18	8.4	3	11.0	-	-	1	3.5
1970	40	7.7	20	9.3	3	11.0	1	4.1	1	3.5
1971	44	8.4	23	10.7	3	11.0	2	8.2	1	3.5
1972	49	9.4	24	11.2	3	11.0	2	8.2	1	3.5
1973	61	11.7	31	14.5	3	11.0	3	12.2	2	7.1
1974	61	11.7	30	14.0	3	11.0	2	8.2	3	10.6

PREVALENCE: NEWFOUNDLAND AND CENSUS DIVISIONS (continued)

Year	5		6		7		8		9		10	
	n	rate	n	rate	n	rate	n	rate	n	rate	n	rate
1965	-	-	1	2.5	2	4.9	2	3.9	3	13.0	-	-
1966	1	2.2	1	2.5	2	4.9	2	3.9	3	13.0	-	-
1967	2	4.5	2	5.0	-	-	2	3.9	3	13.0	-	-
1968	2	4.5	3	7.5	-	-	2	3.9	3	13.0	-	-
1969	2	4.5	4	10.0	-	-	2	3.9	3	13.0	-	-
1970	3	6.7	3	7.5	-	-	5	9.9	3	13.0	1	3.6
1971	4	8.9	3	7.5	-	-	4	7.9	2	8.6	2	7.1
1972	5	11.1	2	5.0	-	-	6	11.8	3	13.0	3	10.7
1973	4	8.9	3	7.5	1	2.5	6	11.8	4	17.3	4	14.2
1974	5	11.1	3	7.5	3	7.4	5	9.9	4	17.3	4	14.2

The number of patients prevalent in each of the census divisions in each of the ten years is shown in Table 31 of the Appendix, p. A-53; a map of census divisions is found in Figure 12 of the Appendix, p. A-15.

3. Mortality

a. Annual Crude Death Rates

Crude rates for Newfoundland calculated for this series are shown in Table 20, p. 166 compared with rates published from Statistics Canada. The summary rates were identical, 1.2 per 100,000 in males and 0.5 per 100,000 in females. Crude and adjusted rates for census divisions and for the provinces are shown in Tables 32 and 33 of the Appendix, pp. A-54-55.

Three year averages were plotted for Canada and for Newfoundland in Figure 6, p. 167. Canadian death rates were consistently higher over the ten year period in both males and females. Since 1972 there has been a gradual but steady decline in the Canadian male death rates (1.6 to 1.5 to 1.4). The same three years have shown an increase in Newfoundland rates in both sexes from 0.9 to 1.0 to 1.4 per 100,000 in males and from 0.5 to 0.7 to 0.8 in females.

b. Comparisons of Adjusted Death Rates

There were 46 deaths from Hodgkin's disease during the ten year period. The SMRs for combined sexes for the

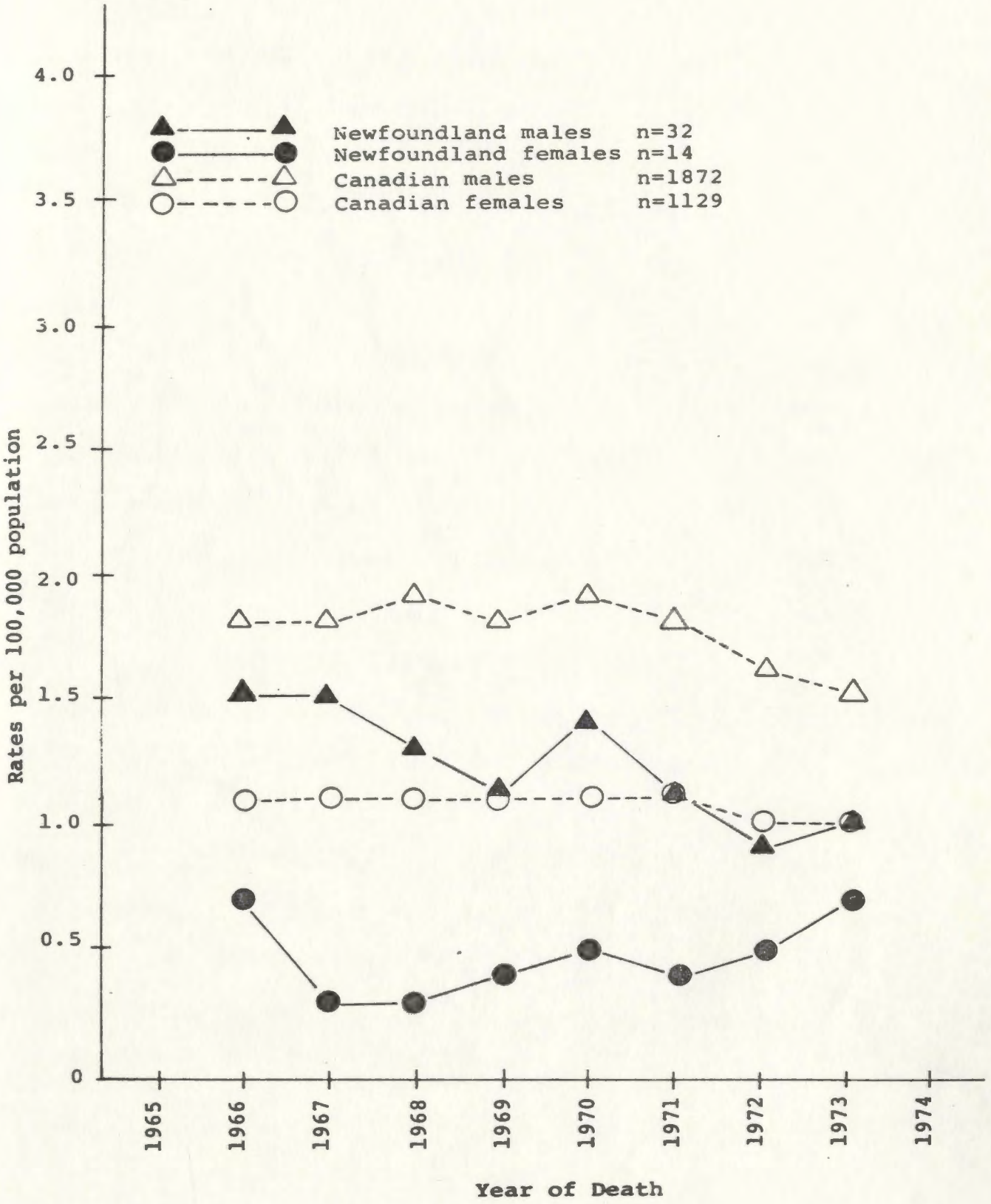
TABLE 20

MORTALITY: CRUDE DEATH RATES, NEWFOUNDLAND, 1965-1974 n=46

		Statistics Canada		This Series	
Year	Sex	n	rate	n	rate
1965	M	2	0.75	2	0.75
	F	3	1.2	3	1.2
1966	M	6	2.3	4	1.5
	F	2	0.78	2	0.78
1967	M	6	2.3	6	2.3
	F	0		0	
1968	M	1	0.38	1	0.38
	F	0		0	
1969	M	3	1.1	3	1.1
	F	2	0.78	2	0.78
1970	M	3	1.1	5	1.9
	F	0		1	0.39
1971	M	3	1.1	3	1.1
	F	1	0.39	1	0.39
1972	M	1	0.38	1	0.38
	F	1	0.39	1	0.39
1973	M	3	1.1	3	1.1
	F	2	0.78	2	0.78
1974	M	4	1.5	4	1.5
	F	2	0.78	2	0.78
TOTAL	M	32	1.2	32	1.2
	F	13	0.5	14	0.5

FIGURE 6

MORTALITY: CRUDE DEATH RATES, THREE YEAR MOVING AVERAGES, CANADA AND NEWFOUNDLAND, 1965-74


Newfoundland males n=32
Newfoundland females n=14
Canadian males n=1872
Canadian females n=1129
Rates per 100,000 population
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
Year of Death

province and census divisions are shown in Figure 7, p. 169. Ratios in census divisions varied considerably. The highest 240 was in Division 9 where there were nearly two and a half times more deaths than expected. There were no deaths in either sex in Labrador, Division 10.

Newfoundland had 80 percent and 63 percent of the deaths predicted by the Canadian rates. The SMRs for Newfoundland and for the other provinces are shown in Figure 8, p. 170. The highest mortality ratio in males was in British Columbia, 116 and the highest ratios in females were in Manitoba and Quebec, 115 and 117. The numbers of observed cases in British Columbia and Quebec were significantly greater than expected ($p = 0.01$). Prince Edward Island had the lowest mortality ratio in males at 68.

c. Age-Specific Death Rates

Age-specific rates for Canada and the provinces are given in Table 34, p. A-56 of the Appendix and plotted in Figure 9, pp. 171-172. A bimodal curve is again evident although the bimodality is less pronounced than in incidence figures. The numbers of deaths were small in most provinces and there were sharp fluctuations in rates. As in incidence, death rates in younger patients were higher in Newfoundland than in Canada as a whole.

FIGURE 7

MORTALITY: AVERAGE ANNUAL ADJUSTED DEATH RATES AND SMRS, CANADA AND NEWFOUNDLAND CENSUS DIVISIONS, 1965-74

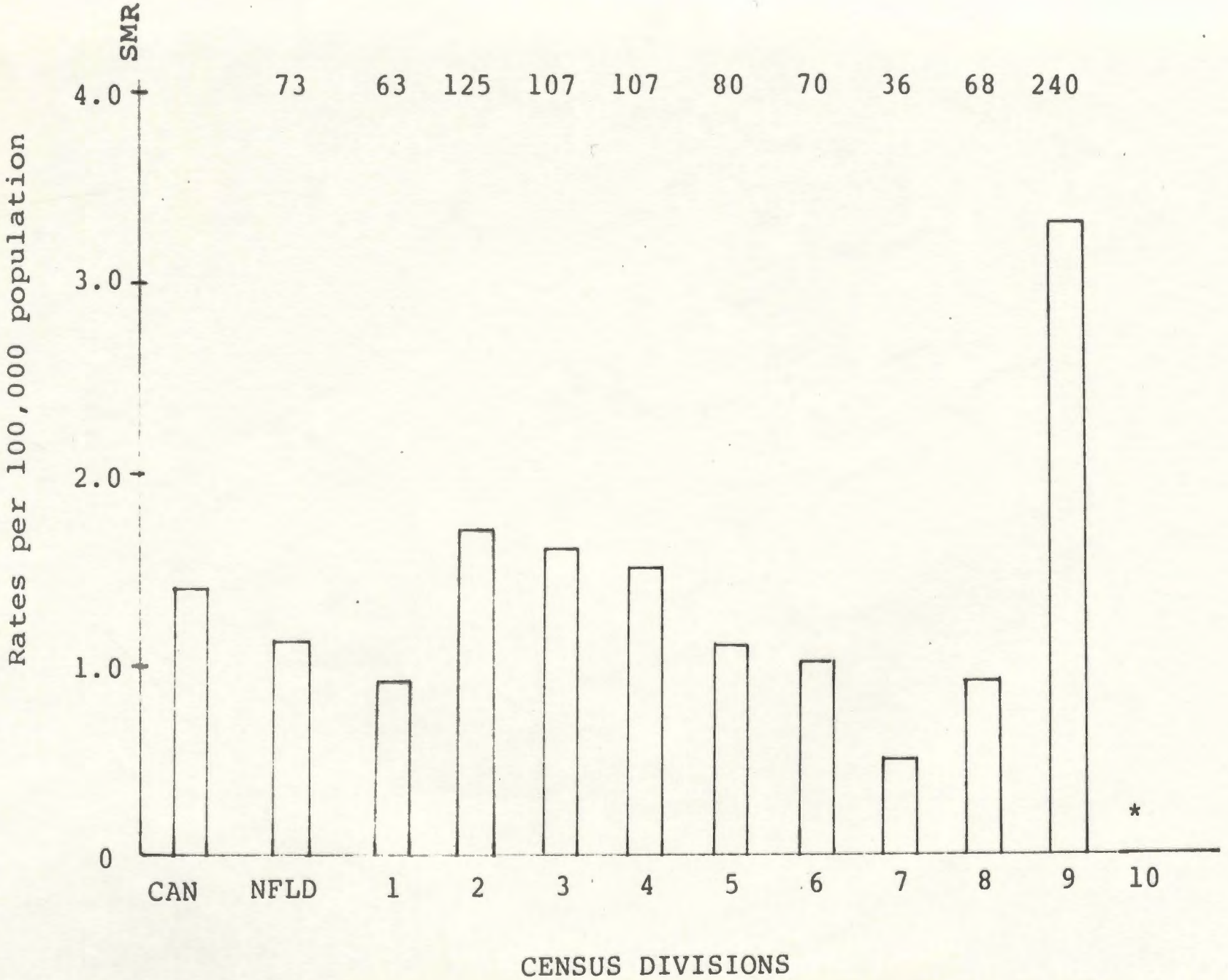

SMR
73
63
125
107
107
80
70
36
68
240
4.0
3.0
2.0
1.0
0
Rates per 100,000 population
*
CAN
NFLD
1
2
3
4
5
6
7
8
9
10
CENSUS DIVISIONS

FIGURE 8

MORTALITY: AVERAGE ANNUAL ADJUSTED DEATH RATES AND SMRS, CANADA AND PROVINCES, 1965-74

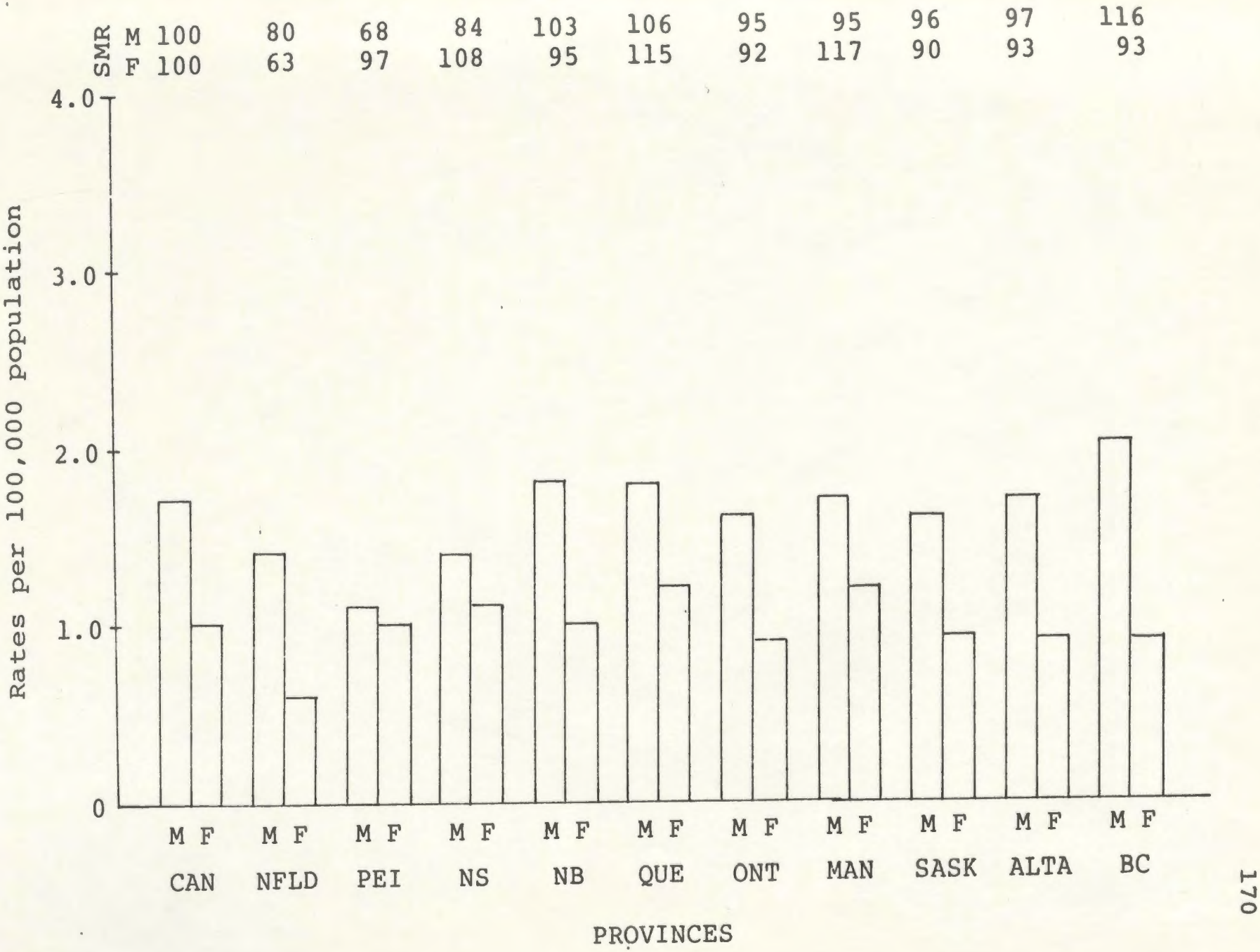

SMR M 100 80 68 84 103 106 95 95 96 97 116
F 100 63 97 108 95 115 92 117 90 93 93
4.0
3.0
2.0
1.0
0
Rates per 100,000 population
M F M F M F M F M F M F M F M F M F M F M F
CAN NFLD PEI NS NB QUE ONT MAN SASK ALTA BC
PROVINCES

FIGURE 9

MORTALITY: AVERAGE ANNUAL AGE-SPECIFIC DEATH RATES, CANADA AND PROVINCES, 1965-74

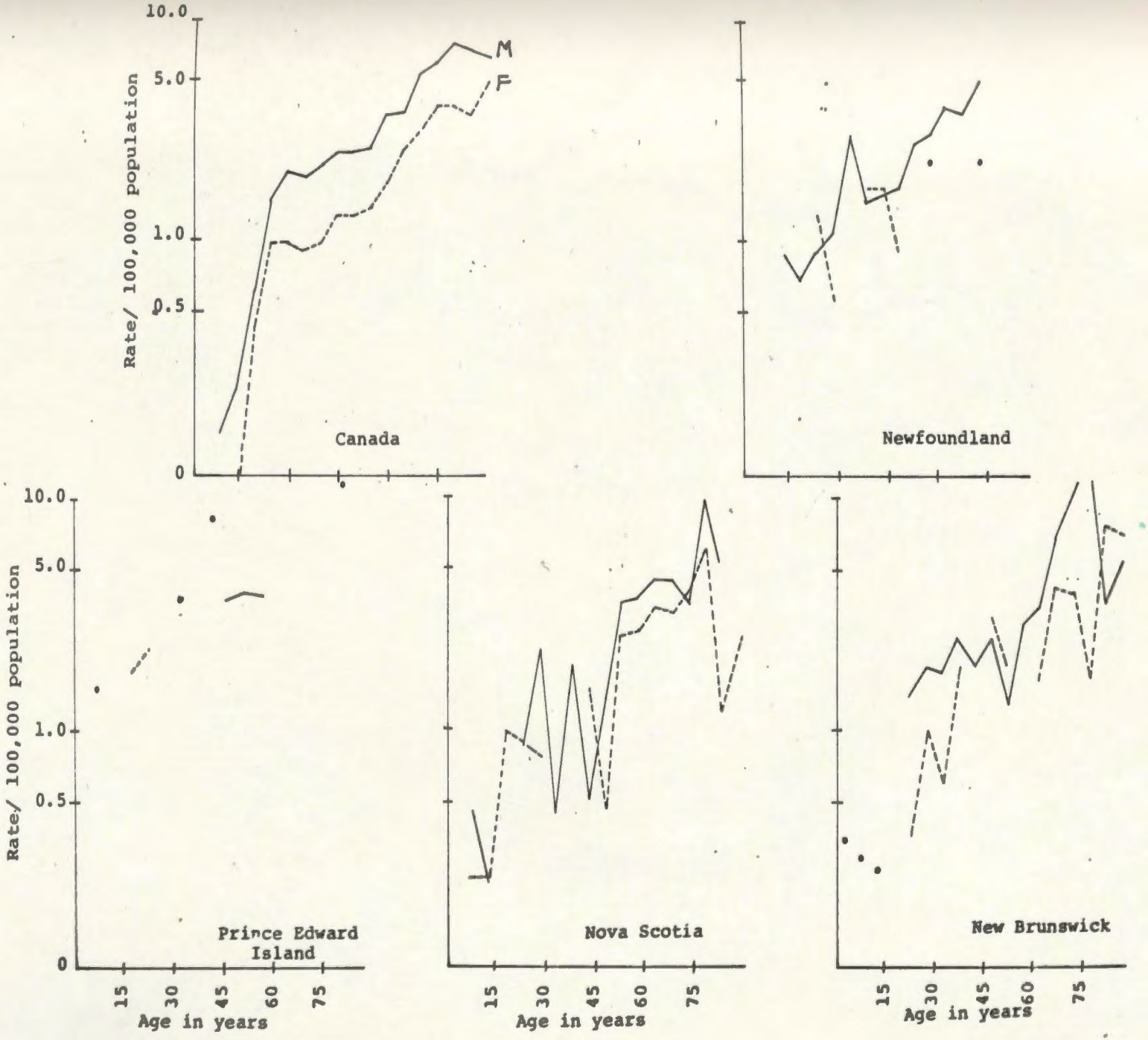
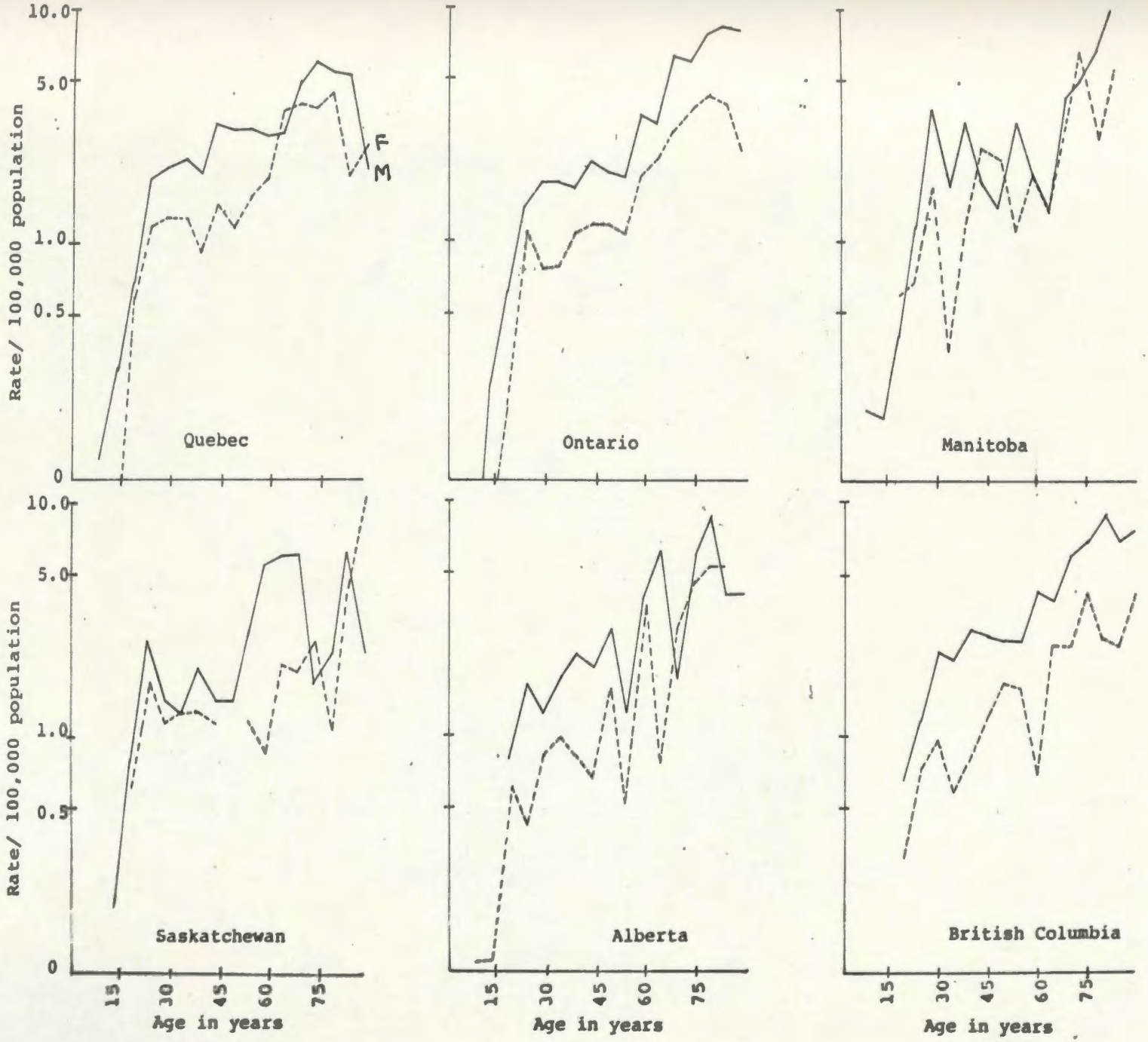

10.0
5.0
1.0
0.5
0
Rate/ 100,000 population
M
F
Canada
Newfoundland
Prince Edward Island
Nova Scotia
New Brunswick
15
30
45
60
75
Age in years

FIGURE 9 (CONTINUED)

MORTALITY: AVERAGE ANNUAL AGE-SPECIFIC DEATH RATES, CANADA AND PROVINCES, 1965-74


Rate/ 100,000 population
10.0
5.0
1.0
0.5
0
M F
Quebec
Ontario
Manitoba
Saskatchewan
Alberta
British Columbia
15
30
45
60
75
Age in years

d. Survival

Survival percentages are given by histopathologic type and by stage in Figure 10, p. 174. Numbers were very small. Overall, five year survivals decreased with advancing stage and in general, patients presenting with no clinical symptoms had better survivals (71 to 50 percent) than those symptomatic at diagnosis (63 to 44 percent).

In the group typed by the Jackson and Parker classification, 40 percent of patients with paragranuloma, 11 percent with granuloma, and none of those with sarcoma were alive at five years. In the Rye group, all of the lymphocyte predominant patients, 73 percent of the nodular sclerosing group, 62 percent and 75 per cent of patients with mixed cellularity and lymphocyte depletion, respectively, were alive at five years. Fifty-three percent of the total patient group were alive at five years. At ten years following diagnosis, 68 percent of the nodular sclerosing group and 51 percent of the mixed cellularity group were still alive (see Table 35 of the Appendix, p. A-57).

Both unstaged and untyped patients showed poor survival rates (34 and 40 percent) indicating that they would, perhaps, have been diagnosed as either mixed cellularity or lymphocyte depletion in advanced stages of disease.

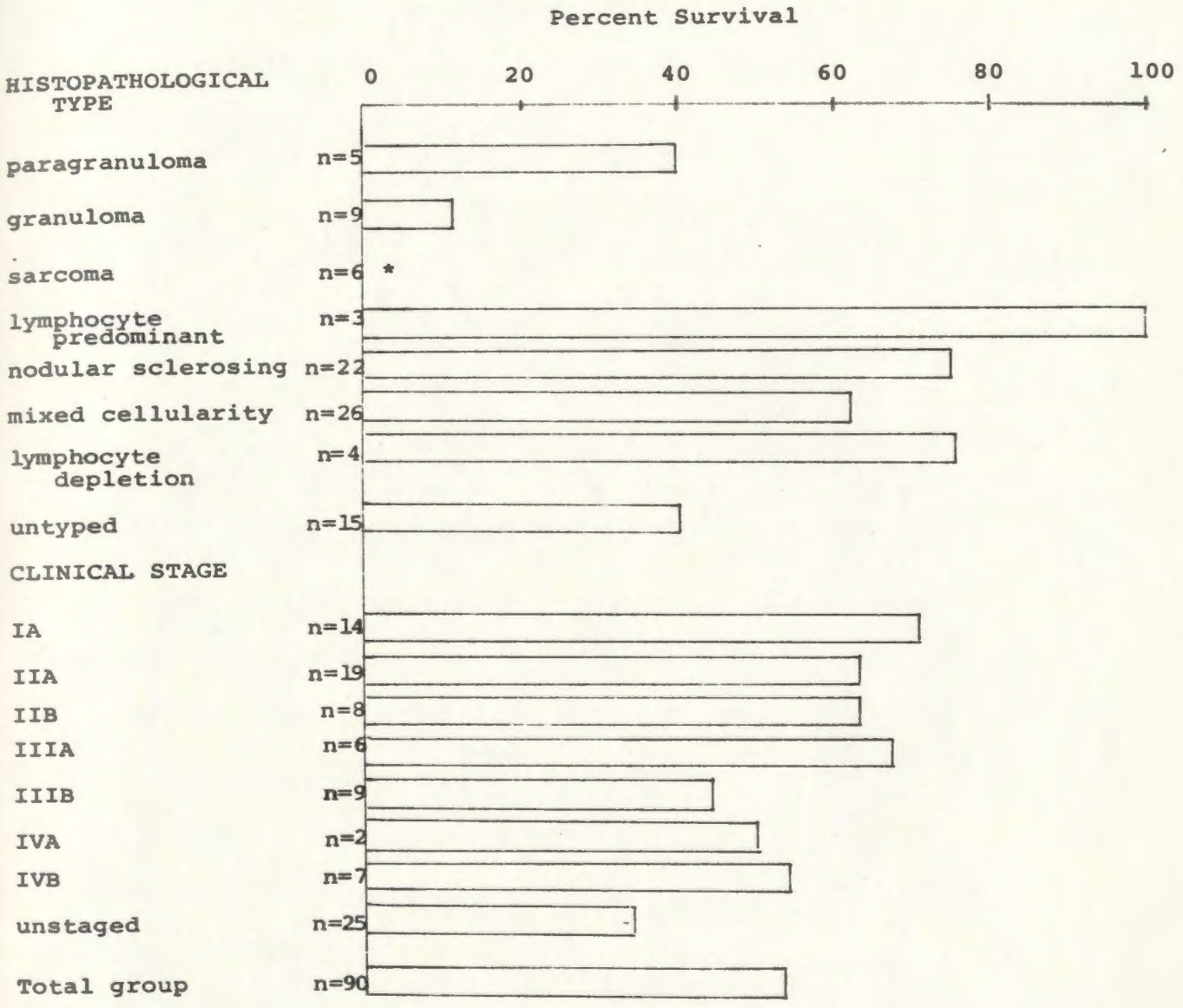


FIGURE 10

SURVIVAL: FIVE YEAR SURVIVAL

4. Geographic Distribution

a. Residence at Diagnosis

The comparison of rates for census divisions was shown earlier (see Figure 2, p. 155 and census division map, Figure 12 of the Appendix, p. A-15). Partly due to small numbers, the distribution of cases across the province was not uniform. The west coast, Division 9, had extremely high rates and other census divisions had fewer than half the expected number of cases.

b. Birthplace

Five patients were born outside the province. Birthplace in Newfoundland was available for 48 of the remaining 85 patients. Although date of birth had been recorded and lack of mobility in this province increased the likelihood that the patient was born in the census division where he or she resided at diagnosis, registrations were not found for the other 37 cases. Birth registration is known to be incomplete in early years and late registration is common.

Using the only data available by census division, i.e. births from 1974 to 1980 to produce expected numbers, births were compared by region across Newfoundland (see Table 21, p. 176). Observed and expected values for single census divisions are shown in Table 36 of the Appendix, p. A-58.

TABLE 21

RISK FACTORS: GEOGRAPHIC DISTRIBUTION OF PATIENT BIRTHS, NEWFOUNDLAND n=48

Census division groups	Observed 1[1]	Expected 2[2]
1	21	19.6
2 + 7	5	6.0
3 + 4 + 5	5	8.4
6 + 8	6	7.8
9 + 10	11	6.3

[1]5 births were outside Newfoundland; birth certificates not found for 37 patients

[2]expected proportions calculated from averaged births, Newfoundland, 1974-1980

$\chi^2 = 5.58$ with 4 degrees of freedom; $p>0.20$

Divisions 9 and 10 showed the greatest deviation from expected values with 11 patient births observed and six expected. There was no significant deviation from expected values in any region.

6. Risk Factors

a. Seasonal Variation in Onset of Disease

Date of diagnosis was equated to date of onset. Cases were tallied by calendar quarter of diagnosis. Assuming no seasonal clustering, equal numbers of cases should be diagnosed in each quarter. The results shown in Table 22, p. 177 show this to be the case. The Chi-square goodness-of-fit test showed no significant deviation from expected values.

TABLE 22

RISK FACTORS: SEASON OF ONSET, NEWFOUNDLAND n=90

Calendar quarter	Observed	Expected
January to March	18	22.5
April to June	25	22.5
July to September	19	22.5
October to December	26	22.5

χ^2 = 2.91 with 3 degrees of freedom; $p>0.20$

b. Seasonal Variation of Birth

The proportion of births of Hodgkin's patients in each calendar quarter was compared to the number expected on the basis of Newfoundland births, 1967 to 1976 (see Table 23, p. 178). The proportion of patient births per quarter differed significantly ($p<0.01$) from expected values. The greatest deviation was in the summer quarter, July to September, with 36 observed births to 23 expected. The corresponding low quarter was the winter period, January to March.

c. Occupation

Thirty-four patients were under 15 years of age, listed as homemakers, or retired and were thus excluded. The proportions of the occupations of the remaining 56

TABLE 23

RISK FACTORS: SEASON OF BIRTH n=89

Calendar quarter	Observed[1]	Expected[2]
January to March	13	22.5
April to June	17	22.5
July to September	36	23.4
October to December	23	21.6

[1]month of birth unknown for one patient
[2]expected proportions calculated from averaged births, 1967-1976, Newfoundland

$\chi^2 = 12.65$ with 3 degrees of freedom; $p<0.01$

patients are compared with proportions of occupations published for Newfoundland and for Canada in 1971 census data in Table 24, p. 179.

There were more patients in educational, professional, clerical, and trades occupations than expected from census data.

Occupations were then grouped into professional, clerical, trades, "unskilled", and "not stated" categories and compared with similar categories from census data (see Table 25, p. 180). Observed numbers were significantly different from expected values. Fewer patients than predicted were employed in processing, materials handling, transport, and the fishing and forestry industries. There were nearly twice as many patients working in the professional, clerical, and construction trades categories as

TABLE 24

RISK FACTORS: OCCUPATIONAL CATEGORIES n = 56

Occupational category	This Study n	This Study percent	Newfoundland percent	Canada percent
Managerial				
Natural sciences	4	7.1	5.5	7.0
Education	5	8.9	4.7	4.0
Medicine	4	7.1	3.9	3.8
Clerical	11	19.6	11.4	15.9
Fishing/Forestry	4	7.1	6.4	1.1
Processing	1	1.8	6.3	3.9
Trades [1]	12	21.4	10.2	6.6
Materials handling	1	1.8	2.9	3.9
Transport	5	8.9	6.4	3.9
Not stated	9	16.1	9.8	8.5
Preschool child	3		NA	NA
School child/student	18		NA	NA
Homemaker	12		NA	NA
Retired	1		NA	NA
Total	90			

[1] 6 of the 12 tradesmen were in carpentry or construction

there were general members of the Newfoundland workforce. There were also more patients for whom no occupation was stated than in the workforce.

TABLE 25

RISK FACTORS: COMPARISON OF OCCUPATIONS n=56

Occupational Category	Observed	Expected[1]
A. Professional Education Medicine	13	7.9
B. Clerical	11	6.4
C. Trades	12	5.7
D. Fishing/forestry Processing Materials handling Transport	11	12.3
E. Not stated	9	5.5

[1]expected values calculated from Newfoundland 1971 census

χ^2 = 15.91 with 4 degrees of freedom; $p<0.01$

c. Urban-Rural Distribution

In some countries, a higher incidence of Hodgkin's disease in females has been found in urban areas and a lower incidence in males in rural regions. The proportions of urban and rural residence according to Statistics Canada are given in Table 26, p. 181. The region of highest incidence, Division 9, had the highest proportion of rural settlement, 79 percent. An east-west trend was observed in incidence for combined sexes.

TABLE 26

RISK FACTORS: PROPORTIONS OF URBAN AND RURAL POPULATIONS CANADA AND THE PROVINCES, 1971 [1]

Region	Percentage Urban	Percentage Rural	Incidence Combined Sexes
Newfoundland Census Divisions			
1	63.5	36.5	1.8
2	59.9	40.1	1.7
3	59.8	40.2	1.9
4	47.8	52.2	2.6
5	71.1	28.9	2.3
6	86.4	13.6	2.1
7	29.8	70.2	1.1
8	29.1	70.9	1.6
9	21.1	78.9	4.1
10	70.6	29.4	1.6
Newfoundland	57.2	42.8	2.3
Prince Edward Island	38.3	61.7	1.6
Nova Scotia	56.7	43.3	2.5
New Brunswick	56.9	43.1	2.5
Quebec	80.7	19.7	2.8
Ontario	82.4	17.7	
Manitoba	69.5	30.5	2.9
Saskatchewan	53.0	47.0	3.0
Alberta	73.5	26.5	3.0
British Columbia	75.7	24.3	3.1
Canada	76.1	23.9	2.8

[1] 1971 census

e. Sibship Size

It has been suggested that risk of Hodgkin's disease increases with fewer siblings. There was a total of 258 siblings recorded for the 40 patients for whom information was available (see Table 27, below). The average sibship size was 6.5 with the number ranging from 1 to 14. If a minimum sibship of one were postulated for the remaining 50 patients, the average sibship for the total patient group would be 3.4. Sibship data is not available for comparisons but the average number of unmarried children living in the family home in Newfoundland in 1971 was 2.4; the Canadian average was 1.7.

TABLE 27

RISK FACTORS: SIBSHIP SIZE	n=40
Total number of sibs noted in records	= 258
Average sibship size	= 6.5
Median number of sibs	= 6
Range of sibship size	= 1 to 14

f. Socioeconomic Status

Using a final set of "socioeconomic" variables for which data was collected in the 1971 census, the incidence rates of Newfoundland census divisions and the provinces were compared with socioeconomic status using stepwise multiple regression analysis. Simple ranking of the regions from low to high frequency of occurrence of

variables (high to low socioeconomic status) had shown no particular pattern in census divisions although Division 9, with the highest incidence ranked in eighth, ninth, or tenth position on a number of variables. Overall, a greater frequency of low ranks (high socioeconomic status) was seen in western provinces and more high ranks (low socioeconomic status) were seen in the Atlantic provinces. The proportions of census variables for each of the regions are shown in Tables 28-30 on pp. 184-187.

The correlation matrix of the regression analysis showed two groupings of variables in census division data, one implicating crowding, i.e., number of persons per household, number of persons per family, and number of persons per room, and a second grouping which seemed to deal with "standard of living", i.e., low income, lack of centralized heat, lack of a flush toilet and, at the lower end of the grouping, education (see Tables 38 and 39 of the Appendix, pp A-60-61). In provincial census data, the groupings were slightly different. The three crowding variables were more closely associated with standard of living, that is with lack of hot water and centralized heating and, to some extent, education and income.

There was no association of any factor with the incidence of Hodgkin's disease in Newfoundland females; increasing number of persons per household was significantly associated with male incidence ($p<.01$). Standard of

TABLE 28

RISK FACTORS: SOCIOECONOMIC STATUS, FAMILY VARIABLES [1]

Region	Percentages				
	$\bar{x}$ children per family	$\bar{x}$ family income	family income <$3000	% family heads in laborforce	% family heads with <grade 8
Nfld Census Divisions					
1	2.2	7332	19.4	24.8	44.0
2	2.5	5606	23.9	30.8	65.5
3	2.5	5289	26.2	25.8	71.0
4	3.2	5659	29.8	34.4	53.3
5	2.5	7692	15.3	21.4	48.4
6	2.5	8031	11.0	17.5	40.8
7	2.1	4625	37.5	36.8	69.6
8	2.6	4834	34.3	33.1	68.6
9	2.9	4556	36.4	72.9	35.1
10	2.4	9501	16.6	35.3	19.0
Nfld	2.4	6680	23.0	26.7	52.2
PEI	2.0	6989	19.0	20.7	46.5
NS	1.8	7858	14.6	20.9	38.5
NB	2.0	7479	15.9	21.6	51.8
Que	1.9	9260	11.2	23.1	50.2
Man	1.7	8646	15.0	17.7	39.0
Sask	1.8	7328	22.1	18.5	44.7
Alta	1.8	9475	13.2	14.4	30.4
BC	1.6	10019	10.0	17.3	27.9
Canada	1.7	9600	11.3	18.1	39.3

[1] 1971 census

TABLE 29

RISK FACTORS: SOCIOECONOMIC STATUS, HOUSEHOLD VARIABLES[1]

Region	Percentages	
	$\bar{x}$ persons per household	%households with 2+ families
Nfld Census Divisions		
1	4.4	5.5
2	4.7	6.1
3	4.9	8.0
4	5.2	4.1
5	4.8	6.4
6	4.7	5.0
7	4.4	8.3
8	4.8	6.3
9	5.2	7.4
10	4.8	5.4
Newfoundland	4.6	6.0
Prince Edward Island	3.9	3.1
Nova Scotia	3.7	3.0
New Brunswick	3.9	3.2
Quebec	3.7	1.7
Manitoba	3.3	1.4
Saskatchewan	3.4	1.0
Alberta	3.4	1.2
British Columbia	3.2	1.6
Canada	3.5	2.0

1 1971 census

TABLE 30

RISK FACTORS: SOCIOECONOMIC STATUS, HOUSING VARIABLES [1]

Region	Percentages			
	house value <$7500	$\bar{x}$ persons per room	cold water only	no flush toilet
Nfld Census Divisions				
1	33.2	.74	16.1	19.2
2	59.8	.86	35.4	23.9
3	57.9	.86	37.3	30.5
4	59.1	.94	19.4	29.1
5	28.3	.83	21.1	13.8
6	32.6	.84	9.2	9.3
7	72.7	.79	32.4	47.5
8	73.0	.85	28.6	49.9
9	72.4	.87	35.1	46.4
10	55.3	.90	6.9	20.7
Nfld	48.6	.80	20.9	25.7
PEI	40.7	.64	7.1	20.9
NS	35.7	.64	8.9	14.2
NB	42.7	.68	9.0	13.1
Que	19.7	.70	4.9	1.8
Man	17.7	.64	1.6	13.3
Sask	30.9	.63	2.8	21.1
Alta	11.9	.63	1.7	9.3
BC	4.1	.61	1.7	2.9
Canada	13.9	.64	3.3	5.8

[1] 1971 census

TABLE 30(continued)

RISK FACTORS: SOCIOECONOMIC STATUS, HOUSING VARIABLES [1]

Region	Percentages			
	space heater only	no fridge	no freezer	no clothes dryer
Nfld Census Divisions				
1	42.4	11.6	76.0	80.2
2	68.6	26.5	81.8	88.3
3	70.9	30.1	76.0	88.3
4	55.1	25.2	59.6	82.6
5	29.4	10.0	59.4	71.7
6	35.6	6.0	58.4	72.3
7	70.5	31.3	71.9	92.3
8	71.5	34.0	68.3	89.0
9	81.4	62.1	65.5	90.5
10	33.2	22.1	71.1	54.9
Nfld	50.3	19.6	71.1	80.8
PEI	39.0	5.2	70.0	73.9
NS	28.1	2.6	74.7	72.5
NB	32.7	4.0	72.3	68.1
Que	31.9	1.0	77.7	61.0
Man	11.7	2.6	53.7	55.5
Sask	17.4	4.0	38.6	55.2
Alta	12.6	2.8	47.7	50.6
BC	13.3	2.0	61.7	61.2
Canada	18.9	2.0	66.5	59.7

[1] 1971 census

living variables were better predictors of provincial incidence. Not owning a clothes dryer was negatively associated with male incidence ($p=.04$) and ownership of a house valued at less than $7500 was negatively associated with female incidence ($p<.01$).

VI. DISCUSSION

The present study was designed to define the status of Hodgkin's disease in Newfoundland, 1965 to 1974. In all published reports incidence and mortality in this province have been low compared to Canada as a whole. Was this due to underascertainment of cases or were there really fewer cases than expected in this province? If serious problems of ascertainment could be ruled out, how might one explain the consistently lower rates seen in Newfoundland?

In an effort to obtain every case of Hodgkin's disease over the ten year study period, three sets of records were used: death certificates, radiation oncology records, and hospital records. Tumor registry records were available for one year.

A final list of 90 incident patients was compiled. None of the three files covering the whole of the study period was complete. Fifty-three incident cases (59 percent) were missing in the set of death certificates. Six patients (7 percent) were not included in the hospital records and 13 (14 percent) were not included in the radiation oncology file. Certainly no one of these sources would have been adequate for compiling detailed information on all recorded cases of Hodgkin's disease in this province.

A. QUALITY OF DATA

Death records have been a useful starting point in many studies. They are usually centralized, easier than other records to access, and they give a preliminary view of disease impact on a population. Cancer is more likely to be accurately given as a cause of death than, for instance, respiratory disease (Dorn and Moriyama, 1964; Moriyama et al., 1958). In many malignancies death rates can, for all practical purposes, be equated with incidence rates because survival is short and it is unlikely that the patient will die of other causes. This is not true of Hodgkin's disease. Survival in the young and in patients with more benign histologic types is now so long that patients are likely to die of other causes. This is especially true with an increasing number of radiogenic second primary neoplasms which are diagnosed some years after Hodgkin's disease and which are more likely to lead to death. In this series only half of the patients who were diagnosed from 1965-74 died of their disease during the same ten year period. Another seven percent died of other causes. Most reviews of death certificates (Bailar et al., 1962; Reid and Rose, 1964; Treolar, 1956; Waife et al., 1952) have revealed similar problems of ascertainment.

Other records are needed to find all cases. The most obvious source to include in this study was the cancer registry. The Newfoundland registry is population based, regularly reviews charts, and actively follows up patients on the anniversary of diagnosis; but information was available for only one year, 1974. The six registry records for 1974 were the only complete set of records in this series; no cases diagnosed in this year had to be excluded and no cases were found in other files that should have been included. The information currently being collected by the registry is much more detailed. In future, these records should include all the information needed for a basic review of the epidemiology of any cancer in Newfoundland.

Since one year of registry records was not sufficient for checking against all of the death certificates, the radiation oncology file which served as the early cancer registry was included. In the case of Hodgkin's disease where treatment combines both radiotherapy and chemotherapy, centralized treatment records were available. For the whole of the study period these records were the most complete. The information requested from patients being treated was fairly detailed, copies of reports and correspondence were kept, and the files were frequently updated as patients came back for check-ups or were followed by mail or by telephone. When stage and type were missing in

these records, it was assumed that staging and classification had not been done. One of the disappointments in using this file was that the National Cancer Institute standard form which had been carefully filled out in the earlier part of the study period had fallen into disuse. It brought together most of the information needed for a basic epidemiological review.

While death certificates, registry, and treatment records provided a great deal of information, certain variables such as birthplace, family history, and occupation were more likely to be found in hospital records. It had been assumed that most patients would be seen in St. John's at the General Hospital where the treatment facilities are centralized. But nearly a third of patients had had only one admission to any hospital in the five to ten years following diagnosis. As longer survivals are attained, one would expect still fewer admissions increasing the likelihood of missing cases using only hospital records. At this time computer listings of inpatient information which were used for auditing purposes and which could supplement Department of Health lists were available in five hospitals; only one hospital coded outpatient records for computer storage.

Some mention must be made of the variability of record keeping aside from the several charting systems used. The most efficient and organized records department

was in the 245 bed regional hospital in Corner Brook. All records and reports were securely fastened in chart folders and a summary list of all admissions with separation diagnoses was uppermost in the chart. Although old charts were stored some distance away in another building, every record requested was found. Outpatient charts were available by diagnosis and, with the hospital's own diagnostic listing, provided useful supplementary information. All pathology reports from this hospital were immediately available.

In the three large hospitals in St. John's, 356 beds, 355 beds, 196 beds, and the Janeway Children's Hospital which has 248 beds, record keeping was much more variable in quality. The Grace Hospital had an excellent alphabetic card file listing the date and separation diagnosis for each admission of that patient; but completed admission files were routinely microfilmed which meant considerable hours of microfilm reading to assemble all of the records for one patient. At St. Clare's Mercy Hospital all admissions were compiled before microfilming making review much easier. There were also fewer records to review since only the charts of deceased or relocated patients were filmed. St. Clare's routinely collected birthplace and mother's maiden name, two seldom requested identifiers. The Janeway Hospital produced microfiche of records of deceased patients, of patients who had moved away, and of patients

who had reached their seventeenth birthdays. These were readily available but in some cases the admissions had not been filmed in chronological order. And, while other hospitals used a standard, recognizable form for pathology reports during this period, the Janeway did not, making it difficult to locate in a thick chart. On the other hand, this hospital collected detailed information on parental occupation, family and social history, and details of previous illnesses.

The General Hospital records had suffered from a series of charting systems and a major move into new premises. A number of older charts were misplaced and, for all practical purposes, lost. Charts containing material from multiple admissions were often disorganized with a number of reports torn loose from the folders. As mentioned earlier, for a brief period pathology reports were not routinely dictated. No written report was available although the results of the examination of biopsy specimens were recorded in the discharge summaries and consultation reports. In more recent years records at this hospital have improved considerably with secure filing of reports within charts, tabulation of admissions, and a more efficient filing and retrieval system. Records in smaller hospitals and cottage hospitals were usually briefer. Since few were typed they were considerably more difficult to read. But these records were useful because

correspondence and reports from larger institutions frequently had been kept together. Also, local medical records staffs often helped in providing missing information. In most instances, they knew the patient well.

The same kinds of gaps and inconsistencies were found in all of the files. Birthplace, occupation, stage and type at diagnosis, and information on pathology were most often missing. Ten percent of dates of diagnoses were inconsistent by over a month which, in a large series, could bias survival results. More serious, 19 percent of hospital insurance numbers did not match the dates of birth they supposedly incorporated. To use the insurance number for linkage of health and vital statistics records, which has been proposed, would seem to be unwise until the insurance file is updated.

In summary, no one set of records would have been sufficient for determining the status of Hodgkin's disease in this province. In a cancer with long survival, a review of death certificates misses too many patients. For those malignancies treated with radiotherapy, treatment records can provide a fairly complete list of patients. Hospital records were the most difficult to use but they provided information found in no other source. In future, tumor registry records would be the logical starting point for basic information.

B. THE EPIDEMIOLOGY OF HODGKIN'S DISEASE IN NEWFOUNDLAND

1. Incidence and Mortality

This study was designed to investigate the supposedly low frequency of Hodgkin's disease in Newfoundland by producing a "complete" list of cases using multiple record sources.

First, it is clear from the final list of 90 cases that both incidence and mortality are lower in Newfoundland than in Canada as a whole. Second, in considering the different incidence patterns of Hodgkin's disease described by Correa and O'Conor in 1973, Newfoundland fits the intermediate Type II pattern of disease with higher risk in the young as well as the young adult and with more cases with poor prognosis. Although a number of family, household, and housing factors associated with low socioeconomic status are in high proportion in this province, it was indication of crowding which was significantly associated with male incidence within Newfoundland. Variables reflecting standard of living were associated with incidence in both sexes in Canada. A third finding of interest was the greater frequency of patient births in the months of July and August. Finally, the west coast patients remain a striking aggregation of Hodgkin's disease in this province.

a. Crude Rates

In the period of this study, both incidence and death rates in Newfoundland were lower than those in Canada as a whole. Incidence rates for Canadian males increased over the last three years of the study from 3.2 in 1971 to 4.0 per 100,000 in 1974. On the other hand, in Newfoundland during the same period, rates for males declined from 3.4 to 2.3 per 100,000. In the latter part of the study period, the mortality curves diverged; Canadian death rates decreased, particularly in males, while Newfoundland rates increased especially in females.

The trend toward higher incidence and lower mortality in Canadian males could be explained by an increasing frequency of new cases more likely to survive long enough to die of other causes; females, particularly those in the nodular sclerosing group, have had long survivals for some time. In Newfoundland, incidence rates in males fell from 1971 to 1974 with an increase in mortality in females. Decreasing incidence in young males and increasing incidence in young adult females with a subsequent increase in mortality would be consistent with a change from a Type II to a Type III pattern.

b. Adjusted Rates

Standard Incidence Ratios (SIRs) for males in two Newfoundland census divisions and for females in five

divisions were extremely low, less than half the number of cases expected were observed. Division 10, Labrador, had no deaths during the study period and incidence ratios were low. This might be explained by a patient from Labrador City-Wabush being admitted to hospital in Quebec; if hospital insurance was not paid by the Newfoundland government there would be no record of an out-of-province admission. But this seems unlikely. Further, no deaths of Newfoundlanders were registered in Quebec during the study period. The low ratios could also be interpreted as due to underreporting from the part of the province geographically most difficult to access. But the presence of the Grenfell Mission nursing stations and hospitals ensured coverage of the Happy Valley-Goose Bay and coastal populations. In the two major urban areas there were medical facilities provided by the air base in Goose Bay and the iron mines in Labrador City-Wabush in addition to community hospitals. In conclusion, it seems improbable that a case of Hodgkin's disease could occur in the Labrador population without the event being picked up on some record. Division 7, Trinity and Bonavista Bays, also had unusually low ratios. However, one regional hospital and two cottage hospitals serve this division; a major hospital and two cottage hospitals lie just on the periphery of the area. Reasonably good roads connected all communities during the study period. The very low incidence and mortality in these two divisions

are puzzling. Were these genetically less susceptible populations or were environmental factors somehow different than in other areas of the province during a critical induction period?

The highest incidence and mortality (SIRs 200, 100; SMR, 240) were in Division 9, the northwest coast. Five of the six male incident cases and five of the six observed deaths in this division were members of a familial aggregation. With their exclusion the incidence ratio would have been 33 in males; the mortality ratio would have been 40. Even though the observed numbers of cases and deaths are within 95 percent confidence limits for chance occurrence, these ratios would have drawn attention to an area with a relatively large number of cases in an otherwise low incidence region.

The Atlantic region had generally lower incidence ratios than any other area of Canada. The western provinces had, on average, high incidence ratios. Male mortality ratios exhibited the same trend, that is, lower in the east and generally higher than expected in the west. Female mortality was higher in the eastern provinces than in the west. The Atlantic provinces appear to be exhibiting a Type II pattern, the Western provinces a Type III pattern.

C. AGE-SPECIFIC RATES

Bimodality of the age incidence curves was clearly seen in Canadian data. Male and female rates paralleled one another with rates in females being considerably lower than those in males. Age-specific death rates in young adults were lower than incidence rates in the same age groups.

The early incidence peak was in the 20 to 29 age group. Mortality overlapped incidence in most provinces.

The age incidence curves of Quebec, Saskatchewan, Alberta, and British Columbia were very much like those first presented by MacMahon in 1957. Low childhood rates, high rates in young adults and high rates in old age are typical of the Type III pattern of Hodgkin's disease. In general, the Atlantic provinces had higher rates in young children, high rates in young adults, and relatively high rates in the elderly, all characteristic of a Type II pattern.

d. International Comparisons

In reviewing international data, crude and adjusted incidence rates (Table 37 of the Appendix, p. A-59) varied considerably from lows of 0.7 and 0.8 per 100,000 in males in Japan and India (Bombay) to 4.0 and 4.1 per 100,000 in Iceland and the United States (Connecticut). World-standardized rates are presented graphically in

Figure 11, p. 214. Canada, with an incidence rate of 3.4 per 100,000, ranked toward the top of the incidence scale in males along with other North American regions and with the very poor regions of Colombia (Cali) and Nigeria (Ibadan) where rates in young males were high. Female rates from Canada (2.1) ranked with Israel and with other North American regions. Newfoundland, on the other hand, ranked in the lower half of the scale. In males, incidence for 1969-74 was comparable to that of the non-Maori population of New Zealand; in females, rural Norway and New Zealand were closest in rank. Incidence rates for 1965-74 placed Newfoundland much lower. Death rates, in general, followed the trend of incidence rates (Table 31, p. 215); they were highest in North America and Europe. Canada's death rate (2.0) was lower than that of Germany and England and Wales but higher than most eastern and African countries. Newfoundland again fell toward the bottom of the scale. With a rate of 1.2 per 100,000, it ranked lower than Canada and Norway but higher than Japan, Mexico, and Hong Kong.

Age-specific rates reflect the incidence patterns described by Correa and O'Conor (1973) (Table 32, p. 216). The lack of young and young adult cases in Japan was most striking. The world-standardized rates of the New Zealand non-Maori group and the rural Norwegian populations were closest to those in Newfoundland but this province had considerably higher rates in the under 20 year old group and lower rates in the middle and older-aged groups indicating,

perhaps, an earlier stage of the Type II pattern. Age-specific death rates paralleled incidence except in the 15-34 year old group where incidence was high and mortality low, reflecting long survivals in the young adult group (Table 33, p. 217).

In summary, Canada fits well into the North American and European group of Type III countries. Newfoundland occupies an intermediate position between this group and the very poor Type I countries.

2. Hodgkin's Disease as a Proportion of all Lymphomas

In this series, Hodgkin's disease accounted for 68 percent of all lymphomas, excluding leukemia, in males under 20 years of age and 16 percent of lymphomas in males over 50 (see Table 34, p. 218). Proportions were similar in data for all of Canada. In international data the geographic patterns described by Correa and O'Conor for the whole of the lymphoreticular group were apparent. In the youngest age group, Burkitt's lymphoma was the major lymphoma in Nigeria (Ibadan), lymphosarcoma was most frequent in Japan, and Hodgkin's disease was more common in North American data. In the middle years, Hodgkin's was the major lymphoma in all areas represented with the exception of Nigeria (Ibadan) where lymphosarcoma accounted for half of the lymphoma group and of Japan where reticulum cell sarcoma was the most frequent diagnosis. In the over

50 year old group, the proportion of Hodgkin's disease had dropped while lymphosarcoma and reticulum cell sarcoma had increased, particularly in Nigeria (Ibadan), Brazil (Recife), Israel, and Japan. In these regions there were proportionately fewer cases of multiple myeloma.

Burkitt's lymphoma is prominent in Africa and lymphosarcoma in Japan in age groups where Hodgkin's disease predominates in North America and Europe. Why geographically different populations of young people should be particularly susceptible to one lymphoma rather than another has not been explained.

3. Sex Ratios

Generally, more male than female cases of Hodgkin's disease are seen in the young with lower sex ratios in the young adult. Newfoundland's ratio was 2.5 under 14 years of age, relatively high, and 1.5 in the 15-24 year old group.

Internationally Hodgkin's disease is more frequent in males except in the young adult group where, in wealthy countries, there are almost equal numbers of cases in males and females (Table 35, p. 219). Higher ratios are found in poorer countries, especially in the youngest age groups.

Newfoundland ratios again fell midway between the Type I and Type III countries.

4. Clinical Stage and Histopathologic Type

The frequency of stage I and II nodular sclerosing disease in American young people was not found in Newfoundland. Twenty-five percent of the youngest patients presented in stages III and IV and 63 percent were mixed cellularity or lymphocyte depletion.

Lymphocyte predominant and lymphocyte depletion disease were two to three times more common in most countries than in Newfoundland. The ratios of generally favorable types (lymphocyte predominant and nodular sclerosis) to those with a poorer prognosis (mixed cellularity and lymphocyte depletion) were low in Colombia (Cali), Uganda, and Norway ranging from 0.29 to 0.67 (Table 36, p. 220). Newfoundland's ratios (0.84 for males, 0.81 for females) were slightly higher but still lower than ratios from the United States (Third National Cancer Survey, Connecticut), Israel, and Japan which ranged from 1.1 to 2.0.

In summary, proportionately more Newfoundland patients had mixed cellularity disease and more young cases presented in stages III and IV than in other North American data. Again, this province occupied a place intermediate to the Type I and Type III countries.

5. Survival

The general trend of greater survival in Stage I disease with decreasing survival through to Stage IV,

holds in both this series and in the Stanford comparison group (Table 37, p. 221). Five year survival was highest in the lymphocyte predominant group and lowest in the lymphocyte depletion group. Numbers are very small for the two extreme groups in the Newfoundland series but in the larger nodular sclerosing and mixed cellularity groups Newfoundland figures were similar to those in the California data.

6. Familial Cases and Clustering

So far, no single factor has been found which explains the increased risk of Hodgkin's disease in certain families of the large Newfoundland kindred although several genetic markers have been associated with patients and patient relatives. Nor has an environmental factor been isolated which may contribute to risk of disease. Thompson's (1982) pedigree analysis has shown that a recessive gene in the homozygous condition could have been shared by all of the cases of Hodgkin's disease and immunodeficiency. This important finding provides evidence for the genetic segment of the etiological network.

Most reports of multiple cases in a family, both foreign and English language, have come from the United States and a few European countries. It is strange that so little has been heard from Scandinavia, England, or South America, all areas where Hodgkin's disease has been

researched with especial interest. One may speculate that perhaps familial Hodgkin's disease is associated with a susceptibility gene which derives from continental Europe and which has not yet spread uniformly across the world.

7. Geographic Distribution

Variations in incidence and mortality across the province were evident. As mentioned in previous discussion, the number of cases in Division 9, the northwest coast, produced an obviously increased rate, 5.9 per 100,000. Nevertheless, the number of observed cases was not significantly different from expected.

When patients were plotted by birthplace a large number of Hodgkin's patients aggregated in Division 9. Again, the number was sufficiently large to attract attention for further investigation but did not exceed expected limits.

The latter analysis may have been biased by the use of births from 1974-80 in Newfoundland to calculate expected rates. We cannot be certain that the distribution of these births from a more recent time period was similar to the distributions that would have occurred in each of the birth years of the patients. Also, birthplace was not available for 45 patients. Nevertheless, the striking rate in

Division 9 would not be seriously diminished by having complete information for the whole series.

The distribution of patients by residence and birthplace adds weight to the notion that the west coast familial aggregation is significant. Aggregation by birthplace tends to favor a genetic etiology but an environmental factor acting very early in development could result in the same sort of distribution.

8. Risk Factors

a. Season of Onset and Season of Birth

Although several studies (Cridland, 1961, Dorken, 1974) had shown a greater than expected number of diagnoses in early fall, late winter, or the 'cold months' of the year, in this series diagnoses were spread evenly over the year.

Season of birth did, however, vary. A greater than expected number of births were found for the July to September quarter. It is of interest that this was also shown in the data of Fraumeni and Li (1969) and of Vianna (1978). Data from Fraumeni and Li (1969) are compared with Newfoundland data in Figure 12, p. 222. While other studies have failed to find an excess in any particular month, no study has found an excess in a month other than July, August, and September.

A seasonally active environmental factor could be implicated which may be involved at one or several points in oncogenesis. The newborn might be exposed to seasonally prevalent allergens or to the first wave of winter respiratory illness. Or, exposure could come weeks later when the baby's own antibodies take over from those of the mother; a delay in production might leave a temporal gap during which the baby could produce only an incomplete response to antigen. This could, perhaps, leave susceptibility to a second challenge at a later, perhaps more vulnerable age. Or, an incomplete response might be maintained as a low level chronic stimulation capable of being triggered by a second environmental stimulus into frank neoplastic transformation. The latter has been suggested by Paffenbarger (1977) as an explanation for the fewer infectious childhood diseases in Hodgkin's patients. Low level chronic response or, on the other hand, a very strong response could prevent clinically detectable disease.

Hormonal fluctuations before or during puberty might also interact with a malfunctioning immune system. Females seem to be somewhat protected in both incidence and type at all ages except in the period just after puberty. If nodular sclerosis disease reflects a strong host response preventing the usual progression of the disease from lymphocyte predominant to mixed cellularity to lymphocyte

depletion, the improved response may somehow be age and stage related.

On the other hand, the putative environmental event could be acting at conception in November or December when some maternal exposure may produce an immune response which can be transmitted to the developing fetus. The subsequent chain of events leading to transformation might begin prenatally or at birth or in pre-adolescence, triggered by an event such as tonsillar involution (Miller et al., 1967) or the hormonal changes at puberty.

b. Occupation

The occupational data collected from this series of patients presented some of the same problems reported in England by Alderson (1972); general categories were reasonably accurate when two records could be compared but minor classifications were occasionally in disagreement. For this reason general categories were used in this study. A greater proportion of cases were in educational occupations and appreciably fewer were in sales, services and processing than would be expected on the basis of the proportions published from the Newfoundland census. By grouping professional, educational, and medical occupations where one might expect persons of higher social class to be employed, there were 13 observed cases to 7.9 expected. Several previous studies have found patients to be more

often employed in professional and skilled occupational categories, confirming the higher risk in higher socio-economic groups (Cohen, 1964; Henderson, 1979; MacMahon, 1966). The proportion of clerical workers in this study was nearly double that found in census data for Newfoundland. MacMahon (1966) also found an excess of clerical workers in his case series. Since the clerical category covers a wide variety of more detailed occupational groups, it is hard to interpret the increased risk for clerical staff. Six of the 12 tradesmen in this series were in occupations with exposure to wood, i.e., carpentry, construction, and sawmill operation. If wood exposure is a risk as has been shown in several other studies, (Greene, 1978; Grufferman et al., 1976; Milham and Hesser, 1967; Petersen and Milham, 1974), one would expect its action to require frequent exposure to high levels of dust or other wood agents. Most men and many women in rural Newfoundland regularly cut wood for heating fuel and a large proportion of men do some logging privately. The majority of an outport population would have been exposed from childhood onwards.

c. Urban-Rural Distribution

There were no clear trends in urban-rural risk of Hodgkin's disease in this study. Greater frequencies of young male patients had been found in rural areas and increased numbers of females in urban areas in Germany and

Scandinavia (Dorken and Singer-Bakker, 1972; Stalsberg, 1973).

d. Sibship Size

In this series, younger patients were from larger sibships than older patients. In contrast, Gutensohn's data from Boston had shown the young adult group to be from smaller sibships than their controls; there was no relation to sibship size in the older age group (Gutensohn, 1982). See Table 38, p. 223.

In the Newfoundland series the group for whom no information on sibship size was available were generally older and therefore more likely to be from larger sibships. If information were available for all of these patients, more large sibships might appear in the older age group; in the two younger age groups, 0-14 and 15-39, where data were more complete, the majority of sibships were quite large.

The increased risk of Hodgkin's disease in persons from smaller sibships is thought to be associated with higher social class. What we are seeing in Newfoundland data appears to be the usual situation of poorer regions. In the youngest age group sibships were very large as would be expected in most poorer populations where childhood incidence is higher. Kirchhoff et al. (1980) found no risk associated with sibship size in Brazil but family size in all groups was high. And in a Portuguese series most cases

were from larger families; childhood incidence was also high in this region (Sobrinho-Simoes, 1978).

e. Socioeconomic Status

Census divisions and provinces were ranked socio-economically using information collected in the 1971 census. No clear pattern was seen in census divisions. Generally, higher socioeconomic status was not associated with higher risk. The northwest coast, Division 9, ranked very low on many variables; on the basis of socioeconomic status, a very low frequency of Hodgkin's would be expected. The occurrence of a very large familial cluster in this environment strengthens the hypothesis for a strong genetic influence in the cases which formed the aggregation.

Provinces ranking higher on the socioeconomic scale for the most part ranked higher in incidence. Newfoundland's low incidence and mortality were reflected in the province's low socioeconomic status.

In summary, international comparisons confirm that the position of Newfoundland in Canada is very like the Type II rural regions of Norway in the generally Type III country of Norway. There are more cases in the young, particularly in males, and a greater frequency of types associated with a poor prognosis. And there are the usual

young adult peak and fewer cases in the old age group. All are characteristics typical of the Type II population.

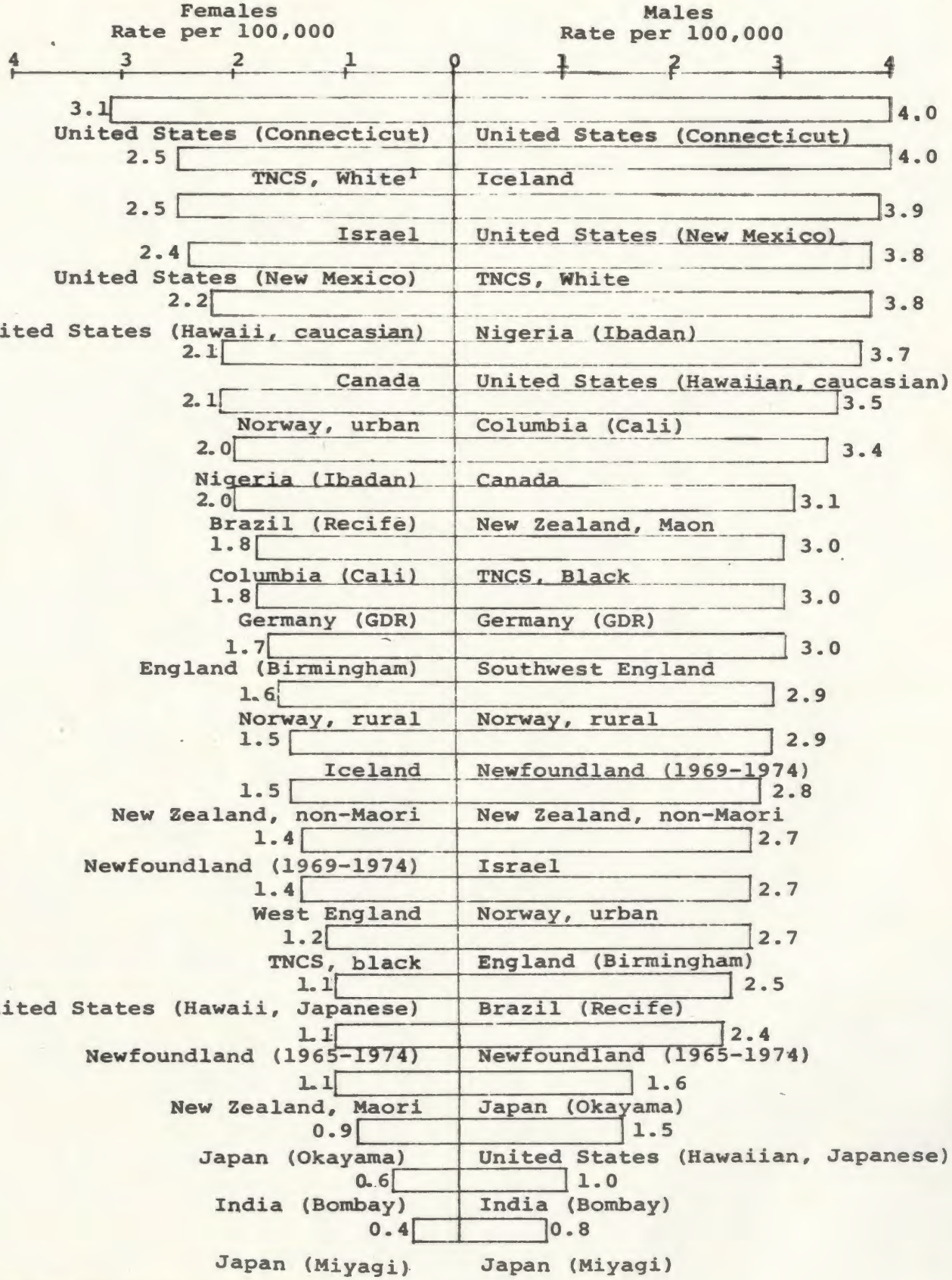
The familial aggregation of Hodgkin's disease is apparent in the distribution of cases by both residence and by birthplace.

More patient births were in July and August suggesting an environmental factor acting at birth or conception.

Professional and clerical workers were at greater risk than persons in other occupations. Younger patients were from larger sibships confirming increased risk in the young in poorer regions. The role of socioeconomic status was further emphasized in the general trend toward high risk in wealthier provinces and lower risk in poorer provinces, including Newfoundland.

FIGURE 11

INTERNATIONAL COMPARISONS: ADJUSTED INCIDENCE RATES



[1]TNCS=Third National Cancer Survey

TABLE 31

INTERNATIONAL COMPARISONS: CRUDE DEATH RATES

Region	Time period	Crude rates per 100,000	
		M	F
This study	1965-74	1.2	0.5
Canada	1965-74	1.7	1.0
Mauritius [1]	1970	0.7	0.0
Mexico	1967	0.4	0.2
U.S.A.	1970	2.0	1.3
Venezuela	1967	0.6	0.5
Hong Kong	1970	0.5	0.2
Israel	1969	1.6	1.1
Japan	1970	0.5	0.2
Germany (GDR)	1970	2.0	1.4
Iceland	1971	1.0	2.0
Norway	1970	1.5	1.2
England and Wales	1970	2.1	1.4

[1] Data from Correa, 1977

TABLE 32

INTERNATIONAL COMPARISONS: AGE-SPECIFIC INCIDENCE RATES

Region		Age Groups																	
		-4	-9	-14	-19	-24	-29	-34	-39	-44	-49	-54	-59	-64	-69	-74	-79	-84	85+	All Ages
This Study	M	.53	-	.50	2.7	6.8	5.7	2.4	1.3	2.7	5.6	4.4	3.2	2.1	8.9	-	-	-	-	2.5
	F	.55	.51	.52	1.7	3.0	3.9	-	1.4	2.9	-	-	3.6	2.3	3.0	3.6	-	8.5	-	1.5
Canada	M	.20	.36	.71	2.6	5.8	5.9	4.5	3.4	3.8	3.9	3.8	5.4	5.6	7.5	7.9	8.2	10.4	5.9	3.4
	F	.05	.28	.87	2.3	3.3	3.3	3.3	1.9	1.9	2.2	2.0	2.7	4.1	4.5	5.0	5.1	3.5	3.4	2.2
United States white[1]	M	0.1	0.6	1.2	3.4	5.7	5.8	3.9	4.6	3.8	4.5	4.8	6.1	7.6	7.2	8.2	11.1	11.5	9.3	3.9
	F	-	0.2	1.1	3.0	4.8	4.2	1.8	2.5	2.0	2.2	3.1	3.1	4.5	6.4	6.1	8.7	4.6	5.2	2.8
black	M	0.3	1.3	1.5	1.8	3.8	3.3	5.2	3.0	3.5	4.7	5.5	4.7	2.0	4.9	7.5	6.8	-	8.7	2.8
	F	-	-	0.5	0.6	1.3	0.8	0.5	-	3.9	3.7	1.8	1.4	-	4.1	4.6	5.1	-	-	1.1
Nigeria (Ibadan)[2]	M	0.3	1.4	2.2	2.7	0.6	1.0	2.3	2.4	4.5	6.8	6.5	7.7	19.7	15.3	9.3	-	-	-	2.0
	F	-	0.3	0.4	0.5	0.2	0.7	0.8	1.4	-	6.8	-	5.0	23.5	-	-	-	-	-	0.9
Columbia (Cali)	M	1.0	1.4	1.7	1.6	2.9	3.3	9.1	1.9	1.2	1.6	1.9	2.9	16.4	8.8	6.6	17.5	-	-	2.8
	F	-	0.4	0.4	2.1	1.0	1.8	-	1.8	-	3.9	3.3	4.4	11.7	-	6.6	-	-	-	1.3
Norway rural	M	-	0.4	0.2	1.7	4.0	4.4	4.3	3.4	4.3	3.6	4.2	6.8	4.2	7.7	4.9	5.6	7.2	5.0	3.2
	F	-	-	0.4	1.4	3.1	2.3	1.4	0.7	3.3	0.9	1.8	2.2	3.5	3.3	5.8	6.7	4.5	1.8	1.9
New Zealand non-Moari	M	-	0.4	0.6	1.9	2.2	4.1	2.4	3.1	3.8	4.4	2.7	4.8	5.2	8.1	14.2	15.1	5.0	4.5	2.9
	F	-	-	0.4	1.3	0.7	1.5	0.7	1.8	0.7	2.4	2.9	3.9	5.0	4.4	2.1	5.7	6.0	17.2	1.7
Japan (Miyagi)	M	-	-	-	-	0.6	0.4	0.4	0.4	0.4	0.5	0.6	4.3	3.3	4.2	1.6	2.7	-	18.2	0.7
	F	-	-	-	-	-	-	-	0.3	0.4	-	1.6	0.6	3.7	-	3.7	3.8	-	-	0.4
Japan (Okayama)	M	-	-	1.5	-	-	-	-	-	3.2	2.2	-	2.6	2.8	6.6	21.8	7.9	-	38.2	1.8
	F	-	-	-	-	2.4	1.5	1.6	-	3.2	1.8	2.1	-	-	-	-	12.3	-	-	1.1

[1]Third National Cancer Survey (TNCS)

[2]Cancer Incidence in Five Continents (CIFC)

TABLE 33

INTERNATIONAL COMPARISONS: AGE-SPECIFIC DEATH RATES

Region	Sex	Age Groups							
		15-14	15-24	25-34	35-44	45-54	55-65	65-74	75+
This study	M	0.4	0.6	2.8	1.6	2.1	3.3	2.1	-
	F	-	0.6	0.3	1.7	0.5	0.6	1.0	1.5
Canada	M	0.2	1.0	2.0	2.2	2.4	3.5	5.6	6.6
	F	0.1	0.7	1.0	1.2	1.3	2.1	3.5	3.7
Mauritius	M	-	-	-	5.1	3.1	-	-	-
	F	-	-	-	-	-	-	-	-
U.S.A.	M	0.2	1.2	2.3	2.4	2.8	4.2	6.1	6.8
	F	0.1	0.7	1.5	1.2	1.7	2.1	4.2	4.7
Venezuela	M	0.3	0.3	0.9	1.0	0.7	1.3	1.6	3.9
	F	0.1	0.3	0.2	0.6	0.8	0.6	2.6	-
Japan	M	0.1	0.1	0.1	0.4	0.8	1.5	2.7	3.3
	F	-	-	0.1	0.2	0.3	0.7	1.1	1.2
Germany(GDR)	M	0.2	1.2	2.2	2.1	3.1	3.9	4.6	3.3
	F	-	1.0	1.6	1.4	1.3	2.3	2.8	3.3
Norway	M	-	0.6	0.9	1.9	1.6	3.8	3.5	5.3
	F	-	0.7	2.2	0.5	2.4	0.9	2.3	3.7
England and Wales	M	0.3	1.6	1.9	2.3	2.5	3.9	5.0	6.6
	F	0.1	0.9	1.4	1.2	1.4	2.0	3.3	3.9
New Zealand	M	-	-	4.0	3.1	2.7	11.6	11.6	6.3
	F	-	0.4	1.2	0.7	2.7	8.4	8.4	7.4

TABLE 34

INTERNATIONAL COMPARISONS: HODGKIN'S DISEASE AS A PROPORTION OF ALL LYMPHOMAS[1] BY AGE GROUPS

Age Group	Newfoundland 1965-74	Canada 1969-74	Ibadan		Recife		UICC Cali		Israel		Japan		Norway	
A. 20 Yrs.														
LS[2]	31.6	38.1	5.0	9.0	39.0	56.0	21.0	31.0	33.0	47.0	55.0	73.0	58.0	58.0
RCS			4.0		17.0		10.0		14.0		18.0		-	
BL	-	-	84.0		5.0		11.0		14.0		9.0		-	
HD	68.4	61.5	8.0		39.0		58.0		39.0		18.0		42.0	
MM	-	0.4	-		-		-		-		-		-	
B. 20-49 Yrs.														
LS	25.0	33.2	41.0	68.0	27.0	55.0	27.0	43.0	25.0	55.0	30.0	80.0	17.0	30.0
RCS			27.0		28.0		16.0		30.0		50.0		13.0	
BL	-	-	3.0		-		-		-		-		-	
HD	67.3	59.0	24.0		46.0		49.0		45.0		20.0		63.0	
MM	7.7	7.8	5.0		-		8.0		-		-		7.0	
C. 50+ Yrs.														
LS	46.0	50.1	44.0	71.0	46.0	70.0	35.0	47.0	39.0	83.0	15.0	74.0	18.0	39.0
RCS			27.0		24.0		12.0		44.0		59.0		21.0	
BL	-	-	-		-		-		-		-		-	
HD	15.6	15.9	23.0		30.0		29.0		17.0		15.0		20.0	
MM	38.4	34.0	6.0		-		24.0		-		11.0		42.0	

[1] excluding other lymphomas (202.2) and the leukemias (204.0 - 208.0)

[2] LS=lymphosarcoma (200.0); RCS=reticulum cell sarcoma (200.1); BL=Burkitt's lymphoma (200.2) HD= Hodgkin's disease (201.0); MM=multiple myeloma (203.0).

TABLE 35

INTERNATIONAL COMPARISONS: SEX RATIOS

A. Age at Diagnosis

Age	This study		TNCS		NCI	IUAC				
					Israel	Uganda	Japan	Norway	Cali	Recife
0-14	2.3	1.4	1.8	1.4	1.0	6.5	2.0	-	5.7	2.3
15-19	0.9		1.2							
20-34	2.4	2.2	1.4	1.5	1.4	2.6	2.1	1.5	2.4	2.1
35-49	1.8		1.8							
50-69	3.3	2.7	1.4	1.2	1.0	1.6	2.7	1.3	1.5	1.4
70+	1.5		1.0							
UK	1				-	-	-	-	-	-

B. Histopathological Type

Type	This study	TNCS		NCI	IUAC			
				Israel	Uganda	Japan	Norway	Cali
		w[2]	b					
PG[1]	0.7	0.9	-	-	-	-	-	-
GR	2.0	1.3	6.0	-	-	-	-	-
SA	6.0	1.7	3.0	-	-	-	-	-
LP	2.0	2.8	2.0	1.9	6.7	4.0	1.4	2.4
NS	1.8	1.0	1.3	0.5	2.8	2.0	0.9	5.0
MC	1.6	1.6	1.8	1.3	2.6	5.0	2.5	2.9
LD	3.0	1.3	0.7	1.2	3.2	3.5	1.1	10.0

[1]PG=paragranuloma; GR=granuloma; SA=sarcoma; LP=lymphocyte predominant; NS=nodular sclerosis; MC=mixed cellularity; LD=lymphocyte depletion

[2]w=white; b=black

TABLE 36

INTERNATIONAL COMPARISONS: PERCENT DISTRIBUTION HISTOLOGIC TYPES OF HODGKIN'S DISEASE

Region		Jackson and Parker classification[1]			Rye classiciation[2]				Ratio LP+NS:MC+LD	
		PG	GR	SA	LP	NS	MC	LP	M	F
A. This study	M	14.2	42.9	42.9	5.7	40.0	45.7	8.6		
	F	50.0	50.0		5.0	40.0	50.0	5.0		
n=75	T	25.0	45.0	30.0	5.4	40.0	47.3	7.3	0.84	0.81
B. TNCS[3]										
white	M	10.0	58.4	31.6	27.5	36.9	29.5	6.1		
	F	15.0	60.6	24.4	14.3	52.7	26.2	6.8		
n=985	T	12.2	59.4	28.4	22.1	43.4	28.1	6.4	1.8	2.0
black	M	8.7	78.3	13.0	17.4	39.1	39.1	4.4		
	F	-	75.0	25.0	11.8	41.2	29.4	17.6		
n=67	T	7.4	77.8	14.8	15.0	40.0	35.0	10.0	1.3	1.1
C. NCI[4]										
Japan	M									
	F									
n=166	T	2.0	92.0	6.0	29.5	25.9	38.0	6.6	1.2	
Uganda	M				21.0	11.0	48.0	20.0		
	F				10.0	13.0	58.0	19.0		
n=123	T				18.0	12.0	50.0	20.0	0.48	0.29
Israel	M				25.0	23.0	34.0	18.0		
	F				13.0	45.0	27.0	15.0		
n=161	T				19.0	30.0	17.0	34.0		
United States	M				20.0	39.0	31.0	10.0		
(Connecticut)	F				4.0	48.0	33.0	14.0		
n=367	T								1.4	
D. IUAC[5] Symposium										
Colombia	M				15.0	12.0	48.0	25.0		
(Cali)	F				23.0	9.0	59.0	9.0	0.38	0.47
n=102	T									
Brazil	M				36.0	23.0	24.0	17.0		
(Recife)	F				30.0	32.0	25.0	12.0	1.4	1.7
n=118	T									
Norway	M				15.4	24.6	41.5	18.5		
	F				15.2	37.0	23.9	23.9	0.67	1.1
n=111	T									

[1] PG = Hodgkin's paragranuloma, GR = Hodgkin's granuloma, SA=Hodgkin's sarcoma

[2] LP = lymphocyte predominant, NS= nodular sclerosis, MC = mixed cellularity, LD = lymphocute depletion.

[3] TNCS = Third National Cancer Survey

[4] NCI = National Cancer Institute

[5] IUAC = International Union Against Cancer

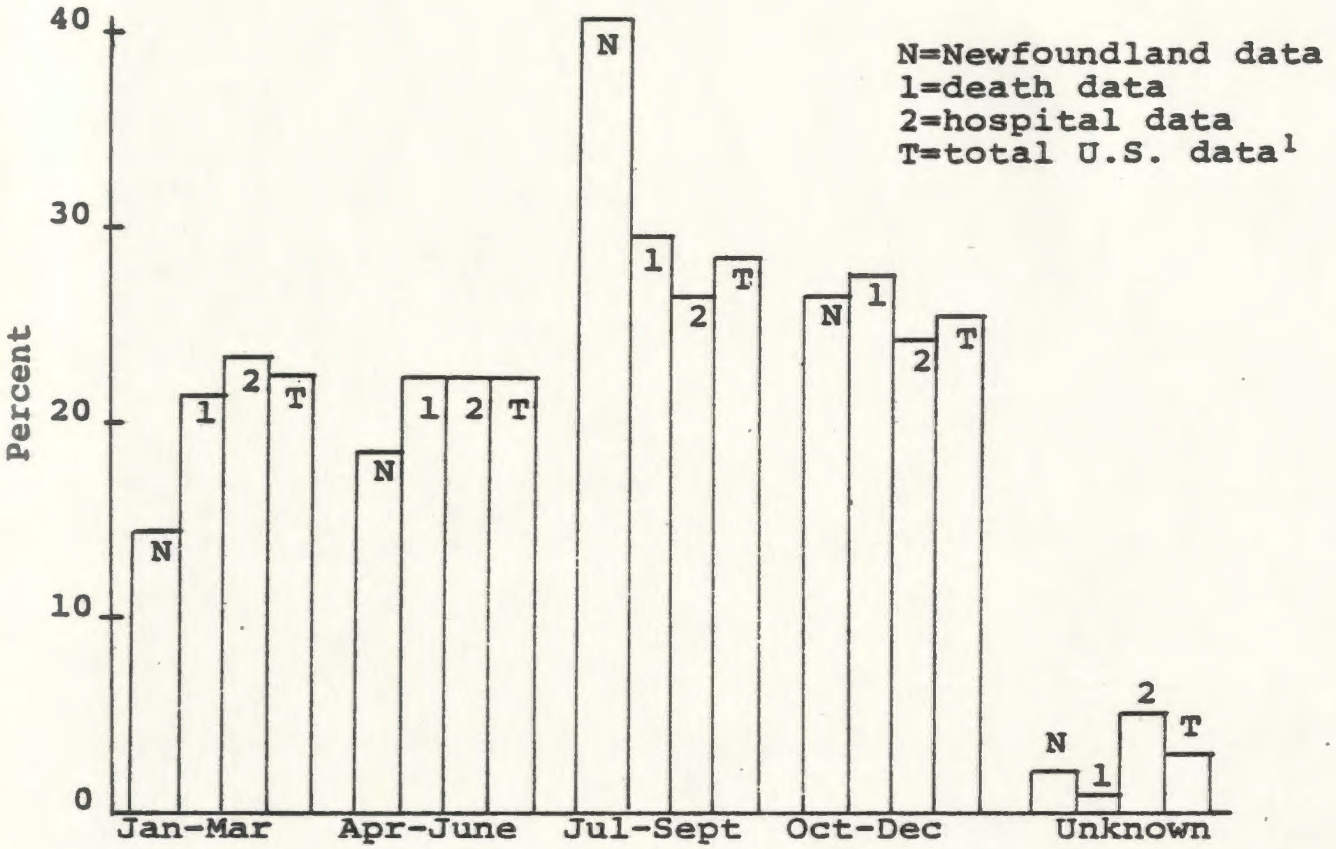
TABLE 37

INTERNATIONAL COMPARISONS: FIVE YEAR SURVIVAL RATES

	This series		California series [1]			
			1961-67		1966-70	
	n	percent	n	percent	n	percent
Stage						
IA	14	71				
I(A+B)			12	83.3	57	86.0
IIA	19	63				
IIB	8	63				
II(A+B)			71	78.9	182	87.9
IIIA	6	67				
IIIB	9	44				
III(A+B)			39	43.6	110	75.5
IVA	2	50				
IVB	7	54				
IV(A+B)			4	25.0	40	40.0
			1961-77			
Type						
LP [2]	3	100	77	95.9		
NS	22	73	820	84.3		
MC	26	62	223	69.8		
LD	4	40	22	26.3		

[1] Data from Kaplan, 1980

[2] LP=lymphocyte predominant; NS=nodular sclerosis; MC=mixed cellularity; LD=lymphocyte depletion



[1] Data from Fraumeni and Li (1969) and this study

FIGURE 12

INTERNATIONAL COMPARISONS: SEASONAL DISTRIBUTION OF BIRTH

TABLE 38

INTERNATIONAL COMPARISONS: SIBSHIP SIZE

A. Cases with sibship information = 40, group 1
Cases without sibship information = 50, group 2

Age distribution of groups 1 and 2

Years of age	Group 1		Group 2	
	n	percent	n	percent
0-14	11	27.5	2	4.0
15-39	19	47.5	26	52.0
40-55	3	7.5	10	20.0
55 +	7	17.5	12	24.0
Total	40	100.0	50	100.0

B. Percent sibship size, Newfoundland and Boston

	Gutensohn study [1] n = 325 Patient Age groups			This study n = 40 Patient Age groups			
Sibship size	15-39	40-54	55+	15-39	40-54	55+	0-14
1-2	34	40	11	11	33	43	-
3-5	53	49	47	26	-	28	36
6+	13	11	43	63	67	29	64
Total percent	100	100	100	100	100	100	100

[1] Data from Gutensohn, 1982

SECTION VII: FUTURE RESEARCH

The apparent complexity of the etiology of Hodgkin's disease makes it difficult to propose appropriate research, particularly in a small population. For example, risk in males is high in childhood, especially in third world countries. And, although risk rises with increasing age, there is a greater increase in females in affluent populations; in wealthy countries young adults of both sexes are at nearly equal risk. Males more frequently present with types of Hodgkin's disease with poorer prognosis while females are somehow protected with an inborn or acquired ability to ward off or consolidate the disease. The crowding and poor socioeconomic status which appear to be part of the greater risk in childhood are associated with lower risk in young adulthood. Virus exposure is likely to be early and thorough in third world countries where children suffer a variety of infectious diseases and are also at higher risk of Hodgkin's disease. On the other hand young adult Hodgkin's patients in wealthier countries are reported to have had fewer diseases of childhood. Whether better nutrition in a higher standard of living has allowed more effective handling of a virus or the lack of disease indicates exposure to fewer playmates in a more affluent childhood is not known. The results of studies of viral antibody and the virus genome in Hodgkin's patients have

been equivocal. Certainly, characterizing the underlying population will be of greater importance in future studies since standard of living has been recognized to affect risk. Documenting changes in risk with changes in socio-economic status will need long term monitoring of incidence data. Meanwhile, factors common to both low and high incidence populations need to be investigated in more detail and confirmed in as many areas as possible. Recent studies have concentrated on confirming and characterizing previously reported risk factors; future research in Newfoundland may help in this effort to narrow and refine the questions asked. For instance, one risk factor which appears to be shared by at least three populations, is the higher risk of persons born in late summer or conceived in the early winter.

The results of this study indicate that Newfoundland is moving from a Type II to a Type III epidemiologic pattern of Hodgkin's disease. The first step in confirming these results is to extend the analysis of Newfoundland material with at least five more years of data. One would expect to see fewer cases of Hodgkin's disease in children and more in young adults with a shift toward nodular sclerosing disease and away from mixed cellularity, particularly in young people.

Second, this study has drawn attention to the higher rates in western provinces where a number of socioeconomic factors infer a higher standard of living and to the lower

rates in the poorer, eastern provinces. This relationship is consistent with the epidemiologic patterns of Correa and O'Conor. To date, only the broad aspects of socioeconomic status have been assessed for the Newfoundland west coast population; a set of 500 questionnaires filled out by household has yet to be analyzed. Information on a number of variables including level of schooling, occupation, water and sewage supply, and the number of persons per household is available in the questionnaire. If a low socioeconomic level is confirmed in this small region of census division 9, the observed high frequency of Hodgkin's disease strengthens the genetic hypothesis; a strong familial component is offsetting the low incidence expected in such an area. Further, patient and non-patient households and high and low incidence communities may be separable with one or a combination of these variables, i.e. patient households or communities with a higher frequency of Hodgkin's may be more strongly associated with crowding, for instance, than with availability of running water or level of schooling.

Third, in this and two previous studies, persons born in the third quarter of the year have been shown to be at higher risk of Hodgkin's disease. If analysis of data now available from provincial cancer registries through Statistics Canada (1969-1979) shows similar results, potential environmental stimuli should be investigated. For

instance, seasonal variation in infectious disease incidence may parallel the peak periods of conception or of birth of Hodgkin's patients; appropriate information should be available from Health and Welfare, Canada. If a climatic influence is involved, one might expect the peak months of birth in the southern hemisphere to be January and February; inquiries have been made to the Tasmanian cancer registry for dates of birth of Hodgkin's patients there.

Finally, all analyses in this study are based on relatively small numbers. A collaborative case-control study in the Atlantic provinces might provide sufficient numbers to contrast socioeconomic groups and age groups. Previous history of childhood diseases as provided by questionnaire could be confirmed by antibody titers; there may be subpopulations of patients who have detectable antibody but who have no clinical history of disease. Other variables which have been looked at in the Boston and Brazil studies, i.e., previous history of warts or fever blisters, sibship size, birth order, and tonsillectomy would also be of interest.

Three of the above projects involve only special listings of available data or analysis of published data. The results of these projects would refine the questions that could then be asked in the latter, more extensive, case-control study. Whether such a collaborative project

involving four cancer registries would be feasible is difficult to say but certainly detailed information from a low incidence region would be a valuable complement to data from the major centers currently working on Hodgkin's disease. Confirmation of their results in a contrasting population would strengthen the socioeconomic hypothesis.

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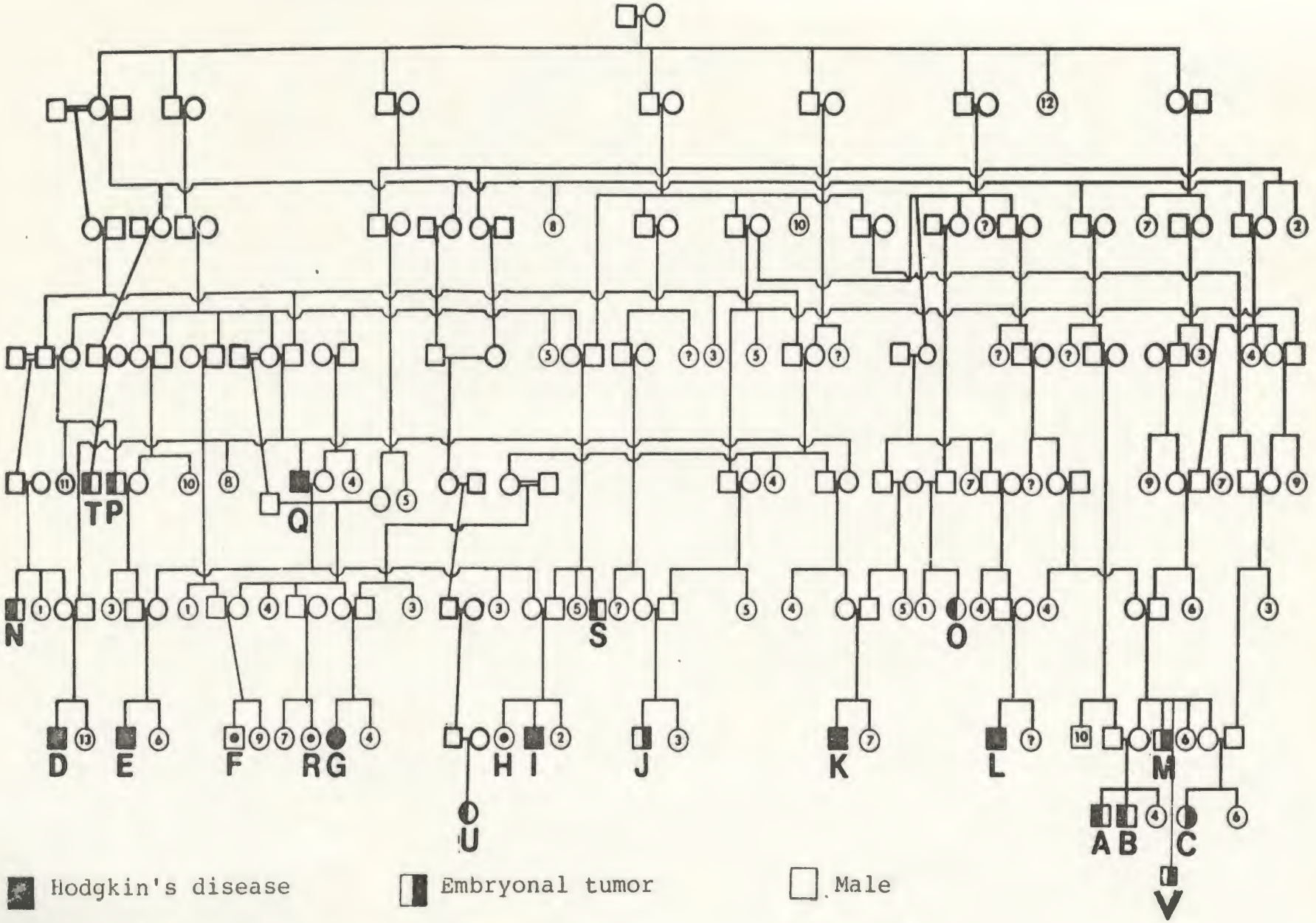
FIGURE 1, APPENDIX

INTRODUCTION: ABRIDGED PEDIGREE OF WEST COAST FAMILY


TP
Q
N
S
O
D
E
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RG
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I
J
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L
M
U
A
B
C
V
Hodgkin's disease
Other lymphoma
Embryonal tumor
Immunodeficiency
Male
Female

TABLE 1, APPENDIX

INTRODUCTION: LIST OF PATIENTS ON WEST COAST PEDIGREE

Patient	Sex	Diagnosis	Year of Dx[1]	Age at Dx	Year of Death
1	F	Hodgkin's disease	1954	7	1969
2	M	Hodgkin's disease	1965	20	1965
3	M	Hodgkin's disease	1966	12	1967
4	M	Hodgkin's disease	1966	31	1966
5	M	Hodgkin's disease	1968	8	1970
6	M	Hodgkin's disease	1970	60	1971
7	M	Hodgkin's disease	1973	10	1976
8	M	Malignant thymoma	1960	2	1960
9	M	Benign thymoma	1964	63	1969
10	M	Lymphosarcoma	1972	47	1972
11	F	Lymphosarcoma	1972	64	1973
12	M	Lymphosarcoma	1972	10	1972
13	M	CLL[2]	1975	68	1975
14	F	ALL	1976	2	1977
15	M	AML	1970	80	1970
16	M	Rhabdomyosarcoma	1964	20	1964
17	M	Rhabdomyosarcoma	1978	39	1979
18	M	Neuroblastoma	1965	3	1965
19	F	Retinoblastoma	1970	1	1971
20	M	AID	1973	31	1973
21	F	AID	1974	27	-
22	F	AID	1975	23	-

1 Dx=diagnosis

2 CLL=chronic lymphatic leukemia, ALL=acute lymphatic leukemia, AML=acute myelogenous leukemia, AID=acquired immunodeficiency syndrom

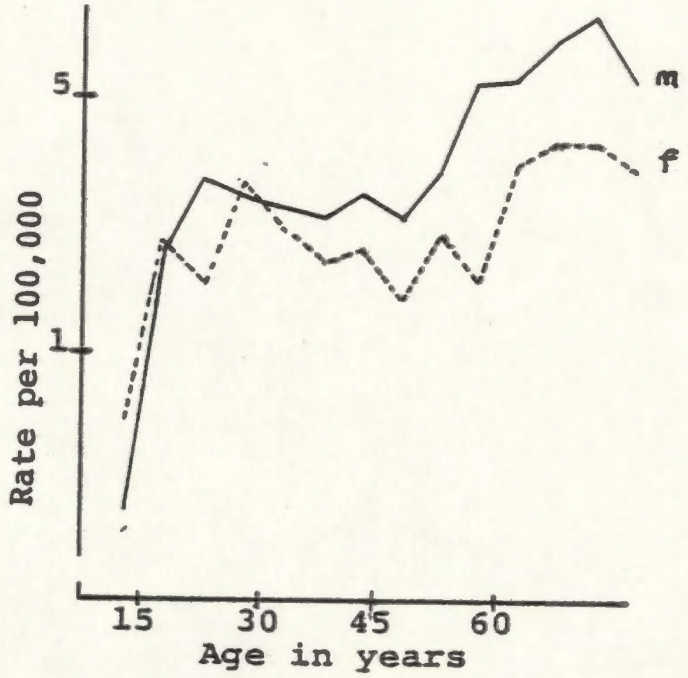
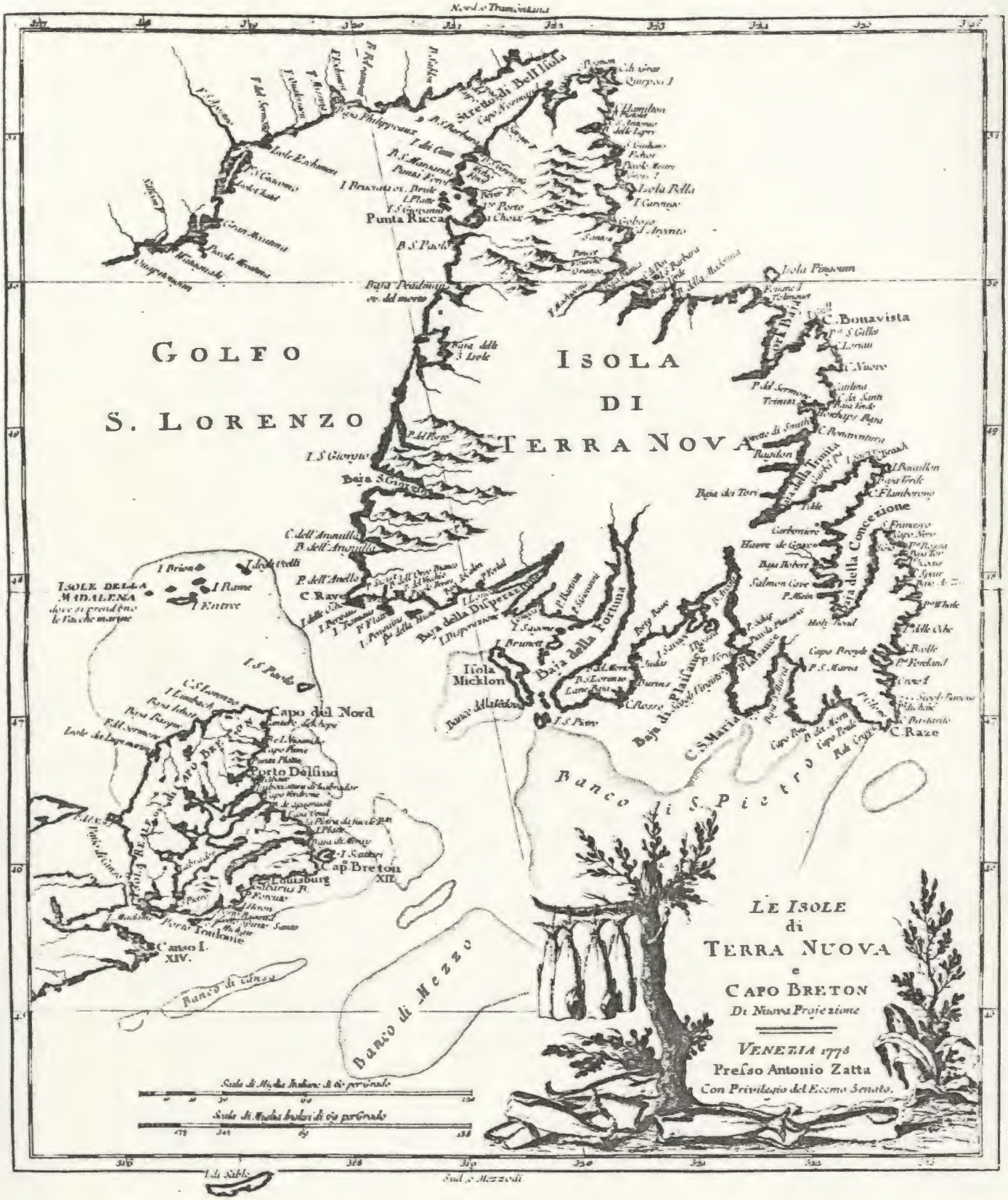


FIGURE 2, APPENDIX

INTRODUCTION: AGE-SPECIFIC INCIDENCE OF HODGKIN'S DISEASE, REDRAWN FROM MACMAHON, 1957

FIGURE 3, APPENDIX

INTRODUCTION: COASTAL SETTLEMENT IN NEWFOUNDLAND, (ZATTA, 1778)


GOLFO
S. LORENZO
ISOLA
DI
TERRA NOVA
Punta Ricca
C. Bonavista
Baja della Trinita
Baja della Concezione
Baja della Fortuna
Isola Micklon
Capo del Nord
Porto Delfino
Cap Breton
Louisburg
Canso I.
C. Raze
C. S. Maria
Banco di S. Pietro
Banco di Mezzo
ISOLE DELLA MADALENA
LE ISOLE
di
TERRA NUOVA
e
CAPO BRETON
Di Nuova Projezione
VENEZIA 1778
Presso Antonio Zatta
Con Privilegio del Eccmo Senato.

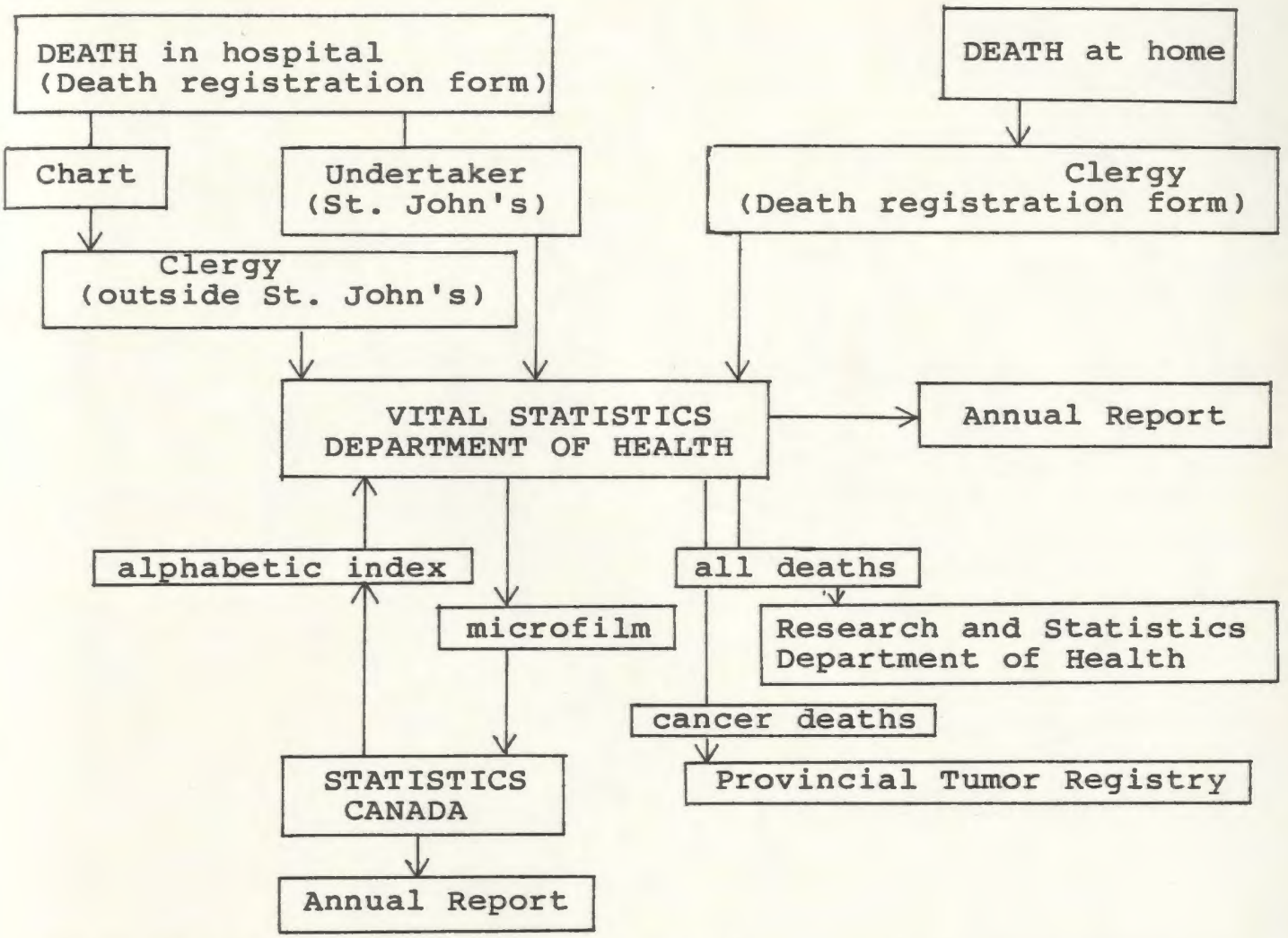


FIGURE 4, APPENDIX

METHODS: RETURN OF DEATH IN NEWFOUNDLAND

FIGURE 5, APPENDIX

METHODS: MEDICAL CERTIFICATE OF DEATH PRIOR TO APRIL 1, 1976

H-620

Department of Health
Vital Statistics Division

GOVERNMENT OF NEWFOUNDLAND AND LABRADOR

Certificate of Registration of Death

1. **Name of Deceased** _____

2. **Residence** _____

3. **Place of Death** _____ | _____
(If in hospital or institution, give date of admission)

MEDICAL CERTIFICATE OF DEATH

4. **I Hereby Certify** that _____

died on _____ 19___ and that to the best of my knowledge and belief the cause of death was as herein stated.

IMMEDIATE CAUSE _____

DUE TO _____

Signed by _____ M.D.
(A registered Medical Practitioner)

Address _____ Date _____

5. Sex	6. AGE in	Years	Months	Days	If less than one day	7. Single / Married / Widowed
		_____	_____	_____	____Hrs. or ____Mins.	_____ / _____ / _____

8. Occupation	9. Birthplace	10. If married give name of husband or maiden name of wife
11. Name of father	12. Maiden name of mother	
13. Place of burial	14. Funeral director	15. Registration Date

A-6

FIGURE 6, APPENDIX

METHODS: MEDICAL CERTIFICATE OF DEATH IN CURRENT USE

FORM H–1

PROVINCE OF
NEWFOUNDLAND (Canada)
Department of Health
Vital Statistics Division
Office of the Registrar General, St. John's

REGISTRATION OF
DEATH

Registration No. *(Department use only)*

THIS IS A PERMANENT LEGAL RECORD
PLEASE TYPE OR PRINT PLAINLY AND COMPLETE ALL ITEMS

This record must be completed and filed with the Registrar General

NAME OF DECEASED
1. Surname of deceased *(print or type)* — All given names *(in order) (print or type)* — 2. SEX — Social Insurance Number *(if available)*

PLACE OF DEATH
3. Name of hospital or institution *(otherwise give exact location where death occurred)* — City, town, or other place *(by name)* — M. C. P. Number

USUAL RESIDENCE
4. Complete address. If rural give exact location *(not Post Office or Rural Route address)* — City, town, or other place *(by name)* — Province *(or country)*

MARITAL STATUS
5. Single, married, widowed, or divorced *(specify)* — 6. If married, widowed, or divorced, give full name of husband or full maiden name of wife

OCCUPATION
7. Type of work done during most of working life
8. Type of business or industry in which worked

BIRTHDATE
9. Month *(by name)*, day, year of birth

AGE
10. Age *(years)* — *(Months)* If under 1 year — *(Days)* — *(Hours)* If under 1 day — *(Minutes)*

BIRTHPLACE
11. City or place — Province *(or country)* of birth

FATHER
12. Surname and given names of father *(print or type)*
13. BIRTHPLACE – City or place — Province *(or country)*

MOTHER
14. Maiden surname and given names of mother *(print or type)*
15. BIRTHPLACE – City or place — Province *(or country)*

SIGNATURE OF INFORMANT
16. Signature of informant
17. Postal address of informant
18. Relationship to deceased — 19. Date signed. *(month, day, year)*

MEDICAL CERTIFICATE OF DEATH

24. DATE OF DEATH: Month *(by name)*, day, year — Approx. interval between onset & death

25. CAUSE OF DEATH

Part I
Immediate cause of death (a) ..... *due to, or as a consequence of*
Antecedent causes, if any, giving rise to the immediate cause (a) above, stating the underlying cause last (b) ..... *due to, or as a consequence of* (c) .....

Part II
Other significant conditions contributing to death but not causally related to the immediate cause (a) above .....

26. Autopsy? Yes ☐ No ☐
27. Does the cause of death stated above take account of autopsy findings? Yes ☐ No ☐
28. May further information relating to the cause of death be available later? Yes ☐ No ☐
29. If accident, suicide, homicide or undetermined *(specify)*
30. Place of injury *(e.g. home, highway, place of employment, etc.)*
31. Date of injury?
32. How did injury occur? *(describe circumstances)*
33. I certify that the above named person died on the date and from the causes stated herein: — Signature *(attending physician, medical examiner)*
34. Designation: Last attending physician ☐ Medical examiner ☐ — Date certified: Month *(by name)*, day, year
35. Name of last attending physician or medical examiner *(print or type)* — Address:

Before completing medical certificate, see instructions on reverse

DISPOSITION
20. Burial, cremation or other disposition *(specify)*
21. Date of burial or disposition: Month *(by name)*, day, year
22. Name and address of cemetery or place of disposition

FUNERAL DIRECTOR
23. Name and address of funeral director *(or person in charge of remains)*

For Office Use Only

CERTIFICATION OF DIVISION REGISTRAR
I certify this return was made to me –
at ..... NFLD.
this ..... day of ..... 19 .....
.....
Signature of Registrar General

4–2302–3.17: 17–10–80

FIGURE 7, APPENDIX

METHODS: LOCATION OF HOSPITALS AND NURSING STATIONS, NEWFOUNDLAND, 1971

See key, p. A-9


Flower's Cove
G
St. Anthony
Conche
Roddickton
Port Saunders
D
Baie Verte
Twillingate
C
Fogo
Bonne Bay
Springdale
Botwood
Brookfield
Gander
Corner Brook
C
I
Buchans
C
Grand Falls
Stephenville
Bonavista
P
Old Perlican
CD
Channel
Carbonear
C
C
Burgeo
Come by Chance
D
Bell Island
D
Harbor Breton
Placentia
Markland
P
C
Grand Bank
R
V
Burin
E
D
St. Lawrence
E
D
St. John's

FIGURE 7, APPENDIX (CONTINUED)

METHODS: LOCATION OF HOSPITALS AND NURSING STATIONS, NEWFOUNDLAND, 1971

Hospitals: 1. Government operated

- ◯ general
- △ cottage
- (P) psychiatric
- (CD) chest diseases

2. Other

- □ general
- P □ pediatric
- R □ rehabilitation
- E □ extended care

Operated by

- [C] corporation
- [D] religious denomination
- [G] International Grenfell Association
- [I] industrial company
- [V] voluntary agency

⬡ nursing station

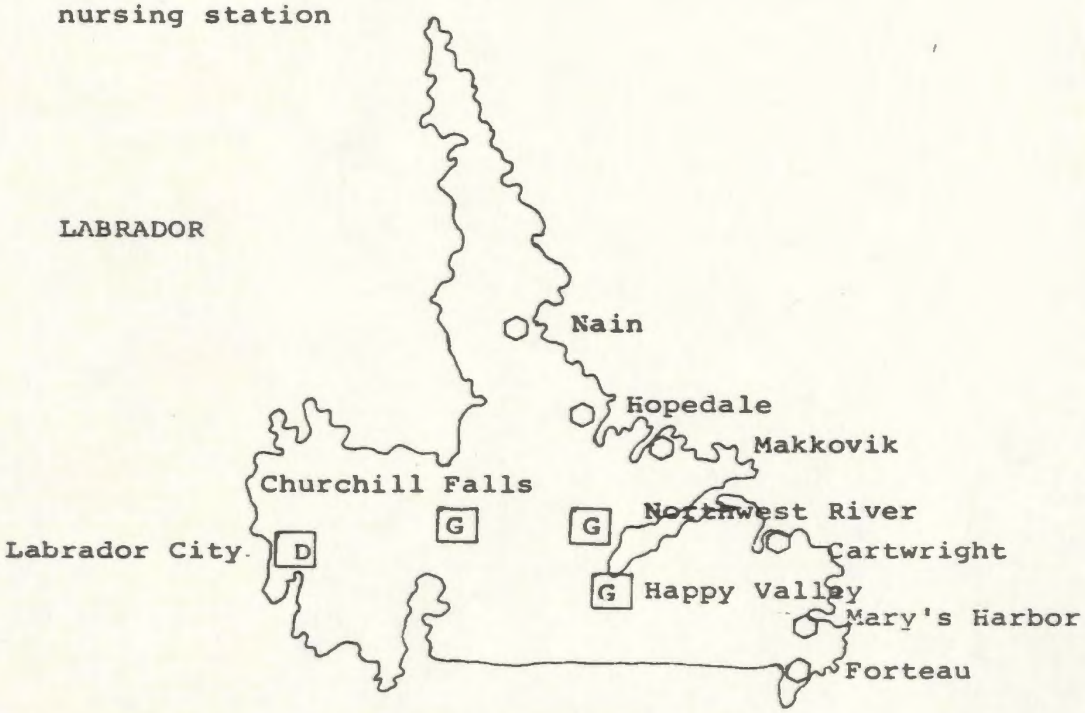


FIGURE 8, APPENDIX

METHODS: ABSTRACT CARD, RADIATION ONCOLOGY DEPARTMENT, GENERAL HOSPITAL

D.D. ☐ D.E.D. ☐ UNT. ☐

YEAR OF DIAGNOSIS 19____ # HAEMIC & LYMPHATIC

CLINIC NUMBER____ PROVINCE____

PHOTO NUMBER____ CLINIC____

PATHOLOGY NUMBER____ PUBLIC PATIENT____ PRIVATE PATIENT____

NAME____

ADDRESS____

DATE OF ADMISSION____

AGE____ SEX____

USUAL OCCUPATION____

FIRST SYMPTOM____

DURATION OF SYMPTOMS (MOS.)____

SEROLOGY: SYPHILIS POS.____ NEG.____

LABORATORY TESTS: DATE OF FIRST EXAM N OF

PERIPHERAL BLOOD____

MARROW____

METASTASES. REGIONAL____

DISTANT____

RECURRENCE (DATE)____

(SITE)____

DATE OF DEATH____

CERTIFIED CAUSE OF DEATH____

PRIMARY: CONTROLLED____ UNCONTROLLED____

POST MORTEM: YES____ NO____

TREATMENT RECORD

RADIATION THERAPY						SURGERY
SITE	DATE	TYPE	TUMOUR DOSE	TOTAL DAYS	TREAT. DAYS	LIST OPERATIONS AND DATES
						CHEMOTHERAPY (DATE)

NOT TREATED BECAUSE: EXTENT OF DISEASE ☐ ASSOCIATED CONDITION ☐ REFUSED ☐

TREATMENT COMPLETED YES ☐ NO ☐

DIAGNOSIS: CLINICAL:

PATHOLOGICAL:

FORM E-12-91 THE NATIONAL CANCER INSTITUTE OF CANADA

FOLLOW-UP RECORD

PERIOD AFTER TREATMENT		CONDITION OF PATIENT						
YEAR	DATE	A.&W.	A.W.D. PR.	A.W.D. SEC.	IND.	UNT.	D.D.	D.E.D.
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								

A. & W. — ALIVE AND WELL.

A.W.D. (PR.) — ALIVE WITH DISEASE AT PRIMARY SITE.

A.W.D. (SEC.) — ALIVE WITH DISEASE AT SECONDARY SITE.

IND. — INDETERMINATE CASE.

UNT. — UNTRACED.

D.D. — DIED OF DISEASE

D.E.D. — DIED OF EXTRANEOUS DISEASE.

MULTIPLE MALIGNANCY YES____ NO____

OTHER SITE

HOSPITALIZATION

YEAR	NO OF DAYS	TREATMENT

ADDITIONAL INFORMATION:

FIGURE 9, APPENDIX

METHODS: ABSTRACT CARD, PROVINCIAL TUMOR REGISTRY

THE NEWFOUNDLAND CANCER TREATMENT AND RESEARCH FOUNDATION

REPORT OF MALIGNANT NEOPLASM

13. Hospital No.: | Chart No.:

14. Attending Physician

1. Reporting province:

2. Insurance No.: *(one only)* Health Ins. No.: | Hospital Ins. No.: | Medicare No.: | Social Ins. No.: | Register Case No.:

3. Name of patient: *(Surname)* *(Given names)* *(Maiden name or other name change)*

4. Residence: *(City, town, village)* *(County, Division)* *(Province)*

5. Birthplace: *(City or place)* *(Country or province)*

6. Sex: 1 ☐ M 2 ☐ F

7. Date of birth: *(day – month – year)*

8. Age:

9. Diagnosis (site):

10. ICDA number:

11. (i) Method of diagnosis
1 ☐ Histo. 1 ☐ Rad. 1 ☐ Clin. 1 ☐ Autopsy
(ii) Date of diagnosis: *(month – year)*

12. Was this case solely discovered from vital statistics records? 1 ☐ Yes 2 ☐ No
If yes indicate death registration no.: _____

CANCER

15. Histology (MOTNAC)

16. Stage T | N | M

Other

17. Multiple primaries Yes | No

18. Initial Treatment

19. Subsequent treatment

DEATH

30. Date Day | Mo. | Yr.

31. Cause

32. Cancer on cert. Yes | No

33. Autopsy Yes | No

Cancer present Yes | No

FOLLOW-UP

	Year	Status
20.	1	
21.	2	
22.	3	
23.	4	
24.	5	
25.	6	
26.	7	
27.	8	
28.	9	
29.	10	

34. SURVIVAL (Mo.)

FIGURE 10, APPENDIX

METHODS: STATISTICS CANADA LISTING OF HODGKIN'S DEATHS REGISTERED IN NEWFOUNDLAND, 1965-74

72	12001017	V2050	12	21	019	1	1	02	St. John's
72	12001042	V2070	12	06	000	1	1	06	
72	12001091	V2079	12	21	019	1	1	26	St. John's
72	12001130	V2022	12	24	000	1	1	04	
72	12001281	V201 X	12	14	007	1	1	52	Corner Brook
72	12001317	V203	12	08	041	2	1	57	St. Albans
72	12001392	V201 X	12	24	000	2	1	59	
72	12001448	V2079	12	01	000	1	1	03	
72	12001681	V209	12	24	000	1	1	62	
72	12001689	V2000X	12	03	005	2	1	41	Channel
72	12001798	V2070	12	21	000	2	1	05	
72	12001861	V2001	12	*19	000	1	1	47	
72	12001870	V2050	12	13	000	1	1	65	
72	12001875	V2041	12	21	019	2	1	61	St. John's
72	12001878	V203	12	18	000	1	1	51	
72	12001910	V203	12	24	000	1	1	65	
72	12001930	V203	12	12	045	2	1	79	Upper Island Cove
72	12002073	V2070	12	15	000	1	1	03	
72	12002084	V203	12	06	000	1	1	76	
72	12002128	V2070	12	21	019	1	1	15	St. John's
72	12002204	V2050	12	08	000	1	1	27	
72	12002225	V2060	12	02	000	1	1	65	
72	12002266	V2001	12	25	000	1	1	20	
72	12002268	V2070	12	16	015	2	1	33	Marystown
72	12002366	V203	12	09	000	1	1	53	
72	12002458	V203	12	14	007	1	1	77	Corner Brook
72	12002470	V2041	12	*19	000	2	1	61	
72	12002535	208	12	14	007	1	1	66	Corner Brook

1964-73 NFLD RESIDENTS (ICC 200-209)
(YR/REGNUM/CAUSE/RESIDENCE/SEX/AGECODE)

72	12002664	V2001	12	14	000	1	1	74	
72	12002766	V2001	12	*19	000	1	1	11	
72	12002777	V2001	12	21	019	1	1	54	St. John's
72	12002943	V2022	12	18	000	1	1	38	
72	12003064	V2001	12	21	019	1	1	57	St. John's
72	12003303	V2070	12	21	016	1	1	04	Mt. Pearl
72	12003322	V2050	12	21	019	1	1	54	St. John's
72	12003821	V2001	12	10	025	2	1	66	Grand Falls
72	12003979	V203	12	06	048	1	1	62	Trepassey
72	12003985	V2050	12	12	045	1	1	26	Upper Island Cove
72	12004014	V2001	12	21	019	1	1	60	St. John's
72	12004267	V2079	12	03	039	1	1	06	Ramea

FIGURE 11, APPENDIX

METHODS: DEPARTMENT OF HEALTH LISTING OF HODGKIN'S DISEASE ADMISSIONS, 1965-74

SELECTION OF RECORDS FROM DEPARTMENT OF HEALTH ADMISSION/SEPARATION MASTER FILE

FOR THE YEARS 1966 - 1971

YEAR	DIAG	-------DESCRIPTION-------	HOSP	CHART NO	ADM NO	DISTRICT	SEX	MCP	AGE	---DOCTORS----		SEP DATE	PRIM DIAGNOSIS	SEC
1966	2010	HODGKIN'S DISEASE	01		06716	09	1		33	000274	000966	240166	2010	1990
1966	2010	HODGKIN'S DISEASE	01		03832	16	1		27	000274	000769	240666	2010	
1966	2010	HODGKIN'S DISEASE	04		00178	08	1		12	000131	000731	100266	2010	
1966	2010	HODGKIN'S DISEASE	38	11443	01337	16	1		27	000769	000987	260566	2010	
1966	2010	HODGKIN'S DISEASE	02		05746	29	1		34	000545	000545	271066	2010	
1966	2010	HODGKIN'S DISEASE	15	0	00105	15	1		67	000882	000882	210266	2010	5760
1966	2010	HODGKIN'S DISEASE	01		06573	06	1		34	000279	000279	041266	2010	
1966	2010	HODGKIN'S DISEASE	03		05458	06	1		47	000205	000205	121266	2010	
1966	2010	HODGKIN'S DISEASE	01		01707	02	1		19	000274	000347	300566	2010	
1966	2010	HODGKIN'S DISEASE	01		03712	29	1		25	000274	000966	240666	2010	
1966	2010	HODGKIN'S DISEASE	01		07240	29	2		59	000336	000336	050366	2010	
1966	2010	HODGKIN'S DISEASE	01		05812	05	2		40	000274	000966	051066	2010	
1966	2010	HODGKIN'S DISEASE	07	0	00399	07	1		16	000198	000198	240866	2010	7888
1966	2010	HODGKIN'S DISEASE	01		01197	09	1		32	000274	000274	300666	2010	6150
1966	2010	HODGKIN'S DISEASE	01		05218	02	1		19	000966	000966	230966	2010	
1966	2010	HODGKIN'S DISEASE	01		05561	07	1		16	000274	000198	051066	2010	
1966	2021	OTHER	55		00949	39	1		00	000144	000144	090666	2021	
1966	2021	OTHER	01		01816	06	2		08	000335	000335	140466	2021	
1966	2021	OTHER	01		07357	16	1		57	000120	000925	220266	2021	
1966	2021	OTHER	26		00488	02	1		19	000961	000961	190366	2021	
1966	2021	OTHER	82		05322	12	1		78	000990	000990	060566	2021	
1966	2021	OTHER	52		00016	38	1		03	000884	000884	130166	2021	2930
1966	2021	OTHER	03		03827	29	2		54	000875	000875	191066	2043	2021
1966	2030	MULTIPLE MYELOMA	49	08895	01649	33	1		63	000184	000184	290666	2030	
1966	2030	MULTIPLE MYELOMA	23	0	01422	23	1		50	000048	000048	061166	4900	2030
1966	2030	MULTIPLE MYELOMA	23	0	00441	23	1		53	000353	000878	020466	2030	4910

FIGURE 11, APPENDIX (CONTINUED)

METHODS: DEPARTMENT OF HEALTH LISTING OF HODGKIN'S DISEASE ADMISSIONS, 1965-74

SELECTION OF RECORDS FROM DEPARTMENT OF HEALTH ADMISSION/SEPARATION MASTER FILE

FOR THE YEARS 1966 - 1971

YEAR	DIAG	-------DESCRIPTION-------	HOSP	CHART NO	ADM NO	DISTRICT	SEX	MCP	AGE	---DOCTORS----		SEP DATE	PRIN DIAGNOSIS	SEC
1971	2010	HODGKIN'S DISEASE	12	10960	00751	135852739	1	779512660035	19	123801	123801	300671	2010	
1971	2010	HODGKIN'S DISEASE	08	01051	00044	144155231	1	149102990012	60	584101	584101	210171	2010	
1971	2010	HODGKIN'S DISEASE	02	95692	06282	167854256	1	349103500014	60	217507	112101	010971	2010	
1971	2010	HODGKIN'S DISEASE	02	93437	01012	237252697	1	589491190015	21	299914	202617	130271	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	01406	144155231	1	149102990012	60	900422	900422	310371	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	01299	232652511	2	699480425015	23	201907	900422	310371	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	00922	135852739	1	779512660035	19	279308	279308	090371	2010	1990
1971	2010	HODGKIN'S DISEASE	01	00000	01038	230952731	2	379290835014	41	363508	297707	090371	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	03952	232952747	1	000000000000	46	279308	310722	240971	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	04035	167854256	1	349103500014	60	234922	234922	030971	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	04511	143054229	1	289191310019	52	363508	363508	221071	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	05006	143054229	1	289191310019	52	363508	363508	161271	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	03541	232952747	1	459251210017	46	279308	279308	260871	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	03809	230952731	2	379290835014	42	279308	279308	230871	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	03521	227652948	1	108902814012	80	217507	686401	280871	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	03321	230952731	2	379290835014	42	363508	363508	060871	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	03191	159854207	1	699231670018	48	217507	363508	280771	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	02766	230952731	2	379290835014	42	363508	363508	260671	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	02930	159854207	1	699231670018	48	363508	279308	020771	2010	
1971	2010	HODGKIN'S DISEASE	01	00000	05714	165454935	2	339123175012	58	279308	279308	240271	2010	2090
1971	2010	HODGKIN'S DISEASE	03	50660	01547	237252697	1	359482440013	22	315707	315707	080571	2010	
1971	2010	HODGKIN'S DISEASE	52	00059	00569	068059088	1	169521200017	19	811507	811507	240771	2010	
1971	2010	HODGKIN'S DISEASE	26	15612	01920	232852681	1	459251210017	46	500701	576701	140771	2010	
1971	2010	HODGKIN'S DISEASE	05	01796	01795	165454935	2	339123175011	59	026301	026301	241171	2010	
1971	2010	HODGKIN'S DISEASE	12	10960	00943	135852739	1	779512660035	19	660901	660901	190871	2010	
1971	2010	HODGKIN'S DISEASE	85	62760	10035	227652385	2	000000000000	11	000094	000094	060571	2010	

FIGURE 12, APPENDIX

METHODS: BOUNDARIES OF NEWFOUNDLAND CENSUS DIVISIONS, (STATISTICS CANADA, 1971)


10
10
9
8
5
6
4
7
3
2
1

TABLE 5, APPENDIX

METHODS: HISTOPATHOLOGIC CLASSIFICATIONS OF HODGKIN'S DISEASE

TABLE 2, APPENDIX

METHODS: EXAMPLES OF COLLATING HOSPITAL ADMISSIONS FOR INDIVIDUAL PATIENTS

	Year	Hospital	Chart No.	Admission No.	District	Sex	MCP[1]	Age
A. Missing record	1970	55	06506	2073	39	1	119071480	63
	1970	82	00000	40541	39	1	000000000	63

May be same patient especially as 39 is a small district with few communities but 55 is not a valid hospital code, 82 codes for Nova Scotia and neither record has enough information to match with a previously identified patient.

B. Questionable record								
	1966	07	00000	00399	07	1	000000000	16
	1966	07	00000	00456	07	1	000000000	16

One previously identified patient with 1950 birthdate from this district; these two admissions assigned to that patient.

1972	85	00000	27687	143054229	2	69926218	46
1972	85	00000	16129	143054229	2	69926018	46

Although 85 codes for an Ontario hospital, the MCP numbers do not match exactly, and the district is a major city, the out-of-province admissions, sex, age and matching date of birth in the MCP number were thought sufficient to assign these two admissions to a previously identified patient with MCP matching on date of birth digits.

1 MCP=medical insurance number

TABLE 3, APPENDIX

METHODS: ESTIMATED POPULATIONS, 1966 AND 1970,[1] AND ENUMERATED POPULATIONS, 1966 AND 1970

Estimated population, Newfoundland, 1966:	495,000
Enumerated population, Newfoundland, 1966:	493,396
Estimated population, Newfoundland, 1971:	524,000
Enumerated population, Newfoundland, 1971:	522,105

[1] Data from office of Statistics Canada, St. John's

TABLE 4, APPENDIX

METHODS: CLINICAL STAGING OF HODGKIN'S DISEASE[1]

A. Development of classifications.

1. Peters (1950): first defined classification for staging; recognized the importance of anatomical extent; distinguished between presence and absence of symptoms (Stages I-III)
2. Rye (1965): separated Stage III involving lymph tissue only into Stages III and IV involving other organs and tissues (Stages I-IV)
3. Peters et al. (1968): distinguished between localized and widely disseminated extra-lymphatic disease; subdivided each stage into symptomatic and asymptomatic (Stages IA-IVB)
4. Musshoff and Boutis (1969): clearly separated A without symptoms from B with symptoms (Stages IA-IVB)
5. Rosenberg and Kaplan (1970): combined earlier classifications; added subscript e to denote single extralymphatic involvement and s to denote involvement of spleen (Stages IA-IVB + e,s)
6. Ann Arbor (1971): clinical stage (CS) clearly separated from pathologic stage (PS);"localized" and "diffused" substituted for "single" and "multiple"; 10 percent weight loss added as a symptom

B. Definition of Ann Arbor staging.

I Involvement of a single lymph node region or of a single extralymphatic organ or site.

II Involvement of two or more lymph node regions on the same side of the diaphragm or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm.

III Involvement of lymph node regions on both sides of the diaphragm which may also be accompanied by involvement of the spleen or by localized involvement of an extralymphatic organ or site or both.

IV Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement.

The absence or presence of fever, night sweats, and/or unexplained loss of 10 percent or more of body weight in the six months preceding admission are to be denoted in all cases by the suffix letters of A or B, respectively.

[1] from Kaplan (1980)

TABLE 5 , APPENDIX

METHODS: HISTOPATHOLOGIC CLASSIFICATIONS OF HODGKIN'S DISEASE[1]

Jackson and Parker (1944)	Lukes, Butler, and Hicks (1956)	Rye (1966)	Distinctive features	Relative frequency %
Paragranuloma	Lymphocytic/histiocytic, diffuse Lymphocytic/histiocytic, nodular	Lymphocytic predominance	Abundant stroma of mature lymphocytes and/or histiocytes; no necrosis; Sternberg-Reed cells may be sparse	10-15
Granuloma	Nodular sclerosis	Nodular sclerosis	Nodules of lymphoid tissue separated by bands of doubly refractile collagen; atypical 'lacunar' Hodgkin's cells in clear spaces within the lymphoid nodules	20-50
	Mixed	Mixed cellularity	Usually numerous Sternberg-Reed cells and mononuclear Hodgkin's cells in a pleomorphic stroma of eosinophils, plasma cells, fibroblasts, and necrotic foci	20-40
Sarcoma	Diffuse fibrosis Reticular	Lymphocytic depletion	Sternberg-Reed cells usually, though not always, abundant; marked paucity of lymphocytes; diffuse nonrefractile fibrosis and necrosis may be present	5-15

From Kaplan, H.S. (1980) Hodgkin's Disease Harvard U. Press: Cambridge

TABLE 6, APPENDIX

METHODS: COMPARISON OF PROPORTIONS OF BIRTHS, ELECTORAL DISTRICTS, 1922, AND CENSUS DIVISIONS, 1974-1980

A. Comparison groups

Division	Electoral district
1	St. John's East and West
	Harbour Main
	Port de Grave
	Harbour Grace
	Carbonear
	Bay de Verde
	Ferryland
	Placentia and St. Mary's
2	Burin
3	Burgeo and LaPoile
	Fortune Bay
4	St. George's
5, 6, 7, 8	Trinity Bay
	Bonavista Bay
	Fogo
	Twillingate
9	St. Barbe
10	Labrador

B. Comparisons

Newfoundland, 1974-1980			1922 Comparison group[1]	
Division	$\bar{n}$	percent	n	percent
1	4062	40.8	3348	45.3
2	580	5.8	272	3.7
3	501	5.0	589	7.9
4	492	4.9	352	4.8
5	3035	30.5	2443	33.0
6				
7				
8				
9	447	4.5	318	4.3
10	842	8.5	70	1.0
Total	9960	100.0	7392	100.0

[1] Data from Vital Statistics Registry, St. John's

TABLE 7, APPENDIX

METHODS: COMPARISONS OF PROPORTIONS OF BIRTHS, CALENDAR QUARTERS, 1922 AND CENSUS DIVISIONS, 1967-1976

A. Proportions

	Calendar quarters				
	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Total
Newfoundland, 1967-1976					
n	29848	30476	31014	28290	119628
percent	25.0	25.5	25.9	23.6	100.0
St. John's					
n	441	437	402	380	1660
percent	26.6	26.3	24.2	22.9	100.0
St. Barbe					
n	122	95	101	98	416
percent	29.3	22.8	24.3	23.6	100.0
Labrador					
n	16	13	16	12	68
percent	25.4	20.6	30.2	23.8	100.0
Total group, 1922 [1]					
n	579	545	522	493	2139
percent	27.1	25.5	24.4	23.0	100.0

B. Comparisons

St. John's	$\chi^2 = 4.68$ [2]
St. Barbe	$\chi^2 = 4.22$
Labrador	$\chi^2 = 1.03$
Total group	$\chi^2 = 5.76$

[1] Data from Vital Statistics Registry, St. John's

[2] Expected proportions calculated from 1967-1976 births

TABLE 8, APPENDIX

METHODS: MAJOR OCCUPATIONAL GROUPINGS, 1971 CENSUS [1]

Major group 11:	managerial, administrative and related occupations.
Major group 21:	occupations in natural sciences, engineering, and mathematics
Major group 27:	teaching and related occupations
Major group 31:	occupations in medicine and health
Major group 41:	clerical and related occupations
Major group 61:	service occupations
Major group 73:	fishing, hunting, trapping and related occupations
Major group 75:	forestry and logging occupations
Major group 81/82:	processing operations
Major group 87:	construction trades occupations
Major group 91:	transport equipment operating occupations
Major group 93:	materials handling and related occupations
Major group 00:	occupation not stated

1 Statistics Canada

TABLE 9, APPENDIX

METHODS: DEFINITIONS OF 1971 CENSUS TERMS[1]

A. Family variables

1. Census family consists of a man or woman with or without children who have never married regardless of age or living with guardianship of a child or a ward under 21 years of age for whom no pay was received or a parent with one or more children never married living in the same dwelling.

2. Children in the family refers to sons and daughters under 25 years of age who have never married and are living at home (including) adopted children, stepchildren, foster children and wards for whom no pay was received (excluding) children ever married living in the same dwelling.

3. Total income (1970) refers to the total income received in 1970 from wages and salaries, business or professional practice, farm operations, family and youth allowances, government old age pensions, other government payments, retirement pensions from previous employment, bond and deposit interest and dividends, other investment sources, and other sources.

4. Family income refers to the sum of the incomes received by all members of the family 15 years old and over, from all sources, during the calendar year 1970.

5. Current labor force is derived by combining those in the groups "worked last week for pay or profit (armed forces) + (civilian)", or "worked last week in unpaid family work", "looked for work last week", "on temporary layoff last week", "with job but not at work last week (armed forces) + (civilian)"....housework in own home and volunteer work are excluded....Also excluded are female farm workers who indicated they helped without pay on a family farm for less than 20 hours a week and inmates of institutions.

6. Level of schooling refers to the highest grade or year of elementary, secondary or university attended.

B. Household variables

Household is a person or group of persons occupying one dwelling. It usually consists of a family group with or without lodgers or employees....

[1] 1971 census, Statistics Canada

TABLE 9, APPENDIX (continued)

METHODS: DEFINITIONS OF 1971 CENSUS TERMS [1]

C. Housing variables

1. Room refers to an enclosed area within a dwelling which is finished and suitable for year round living. Not counted as rooms are bathrooms, clothes closets, pantries, halls, and rooms solely used for business purposes.

2. House value refers to the amount expected by the owner if the dwelling were to be sold to a willing buyer.

3. Water supply refers to water which is piped inside the dwelling and controlled by a tap (hot and cold/cold only/none).

4. Flush toilet refers to a toilet connected to a drainage system and operated by means of water piped into it.

5. Heating refers to principal physical heating equipment regardless of fuel used (hot water furnace/hot air furnace/installed electric heating/ heating stove/ cook stove/ space heater/ other).

D. Urban-rural variables

1. The urban populations included all persons living in 1)incorporated cities, towns, villages with a population of 1000 or over 2) unincorporated places of 1000 or over having a population density of at least 1000 per square mile 3) the built up fringes of the first or second with at least 1000 people and a minimum density of 1000 per square mile 4) the urbanized fringe of 1) or 2).

2. Rural is everything excluded in the definition of urban.

[1] Statistics Canada

TABLE 10, APPENDIX

METHODS: LIST OF REGISTRIES SURVEYED IN CANCER INCIDENCE IN FIVE CONTINENTS [1]

1. Africa
   Nigeria, Ibadan
   Rhodesia, Bulawayo

2. America
   Brazil, Pernambuco, Recife
   Brazil, Sao Paulo
   Canada, Alberta
   Canada, British Columbia
   Canada, Manitoba
   Canada, Maritime Provinces
   Canada, Newfoundland
   Canada, Quebec
   Canada, Saskatchewan
   Colombia, Cali
   Cuba
   Jamaica, Kingston, St. Andrew
   U.S.A., California, Alameda County
   U.S.A., California, San Francisco Bay Area
   U.S.A., Connecticut
   U.S.A., Iowa
   U.S.A., Michigan, Detroit
   U.S.A., New Mexico
   U.S.A., New York State
   U.S.A., Puerto Rico
   U.S.A., Texas, El Paso
   U.S.A., Utah

3. Asia
   India, Bombay
   Israel
   Japan, Miyagi Prefecture
   Japan, Okayama Prefecture
   Japan, Osaka Prefecture
   Singapore

[1] Waterhouse et al., eds. (1976)

TABLE 10, APPENDIX (continued)

METHODS: LIST OF REGISTRIES SURVEYED IN CANCER INCIDENCE IN FIVE CONTINENTS [1]

4. Europe
   Denmark
   Federal Republic of Germany, Hamburg
   Federal Republic of Germany, Saarland
   Finland
   German Democratic Republic
   Hungary, County Szabolcs-Szatmar
   Hungary, County Vas
   Iceland
   Malta
   Norway
   Poland, Cieszyn Area and Nowy Sacz Cieszyn Area
   Poland, Cracow City and District
   Poland, Catowice District
   Poland, Warsaw City
   Poland, Warsaw Rural Areas
   Romania, County Timis
   Spain, Zaragoze
   Sweden
   Switzerland
   U.K., England, Birmingham Region
   U.K., England, Oxford Region
   U.K., England, Sheffield Region
   U.K., England, South Metropolitan Region
   U.K., England, South Western Region
   U.K., England and Wales, Liverpool Region
   U.K., Scotland, Ayrshire
   Yugoslavia, Slovenia

5. Oceania
   U.S.A., Hawaii
   New Zealand

[1] Waterhouse et al., eds. (1976)

TABLE 11, APPENDIX

METHODS: REGISTRIES SELECTED FROM CANCER INCIDENCE IN FIVE CONTINENTS [1]

Region	Population	Period covered	Cases Hodgkin's M	Cases Hodgkin's F	Cases All sites M	Cases All sites F
Africa						
Ibadan	627,400	1960-69	71	23	1184	1197
America						
Recife	1,078,900	1968-71	47	39	1803	2975
Cali	761,000	1967-71	49	26	1455	2484
Connecticut	3,026,700	1968-72	298	266	24168	24250
New Mexico						
white	532,232	1969-72	41	29	3176	3160
Asia						
Bombay	5,537,700	1968-72	129	46	10960	7508
Israel	2,874,100	1967-71	164	156	13557	14614
Miyagi	1,819,200	1968-71	25	16	5982	5162
Okayama	1,707,000	1968-71	15	10	1774	1763
Europe						
Germany(GDR)	17,063,300	1968-72	1346	1059	117862	139345
Iceland	200,100	1964-72	36	14	1930	2269
Norway	3,888,300	1968-72				
urban			127	109	13066	13898
rural			185	105	14382	13447
Birmingham	5,121,500	1968-72	369	251	38474	39452
SW England	3,092,200	1966-70	248	143	24755	28348
Oceania						
Hawaii	767,800	1968-72				
Caucasian			22	12	1223	1326
Japanese			9	7	1283	1196
New Zealand	2,806,100	1968-71				
non-Maori			149	81	12324	11830
Maori			9	5	440	507

[1] Waterhouse et al, 1976

TABLE 12, APPENDIX

METHODS: REGIONS INCLUDED IN IUAC SURVEY OF LYMPHORETICULAR TUMORS,[1,2]

Region	Population	Period covered	Cases Hodgkin's M	Cases Hodgkin's F
Ibadan		1960-66	107	37
Western Nigeria			227	
Argentina	20,759	1949-70	323	188
Brazil	12,866,759	1953-68	274	108
Costa Rica	1,334,174	1960-64	35	12
Peru	10,185,500	1952-70	155	65
Egypt	34,035,000	1960-71	194	
Israel	2,774,559	1967-68	55	47
Singapore		1960-69	63	14
Norway	3,802,479	1968	92	
Papua, NG	2,149,507	1967-71	13	3

1 IUAC=International Union against Cancer
2 Correa et al., 1973

TABLE 13, APPENDIX

METHODS: REGIONS INCLUDED IN NCI SURVEY OF HODGKIN'S DISEASE [1]

Region	Period covered	Cases Hodgkin's M	F
Uganda	1964-68	131	
Connecticut	1935-68	389 (sample)	
Connecticut	1950-68	210	157
Lima	1952-70	155	65
Bogata	1955-70	147	53
Cali	1962-69	78	22
El Salvador	1961-70	112	47
Trujillo	1960-67	18	7
Medellin	1944-69	280	98
Recife	1961-70	88	48
Sao Paulo	1961-70	87	44
San Jose	1960-64	35	12
Buenos Aires	1957-70	313	188
Concepcion	1060-69		
Japan	1958-60		
	1967-69	166	
Israel	1960-68	161	
Europe [2]			

[1] O'Conor, 1973

[2] data from Waterhouse et al., 1976.

TABLE 14, APPENDIX

METHODS: REGISTRIES SURVEYED IN CANCER IN CANADA, 1969-1974 [1]

Registry	Population (1971)	Cases Hodgkin's M	Cases Hodgkin's G	Cases All sites M	Cases All sites F
Newfoundland	522,105	40	23	3453[2]	2558
				1060[3]	
P.E.I.	111,640	8	3	956	850
				305	
Nova Scotia	788.960	73	44	5882	5348
				2221	
New Brunswick	634,560	67	26	5545	4922
				1931	
Quebec	6,027,765	614	380	39799	38463
				15014	
Manitoba	988,250	104	76	9561	8124
				3249	
Saskatchewan	926,245	110	56	10350	7767
				3486	
Alberta	1,627,875	165	124	11866	9999
				3883	
B.C.	2,184,620	253	174	24852	23134
				8578	
Canada	21,568,310	1438	910	113818	102400
				39727	

[1] Statistics Canada
[2] cases for 1970-1974
[3] cases for 1969, combined sexes

TABLE 15, APPENDIX

METHODS: REGIONS SURVEYED IN THIRD NATIONAL CANCER SURVEY, 1969-71 [1]

Region	Population	Cases Hodgkin's M	Cases Hodgkin's F	Cases All sites M	Cases All sites F
All regions	21,003,451	1159	846	90921	90106
Atlanta	1,390,164	64	43	4531	4810
Birmingham [2]	739,274	35	12	3209	3034
Colorado	2,207,259	89	71	8099	8029
Dallas [2]	2.318,036	117	86	8878	8482
Detroit [2]	4,199,931	208	158	17791	16818
Iowa	2,824,376	170	124	13,861	13557
Minneapolis [2]	1,813,647	108	76	7291	7902
Pittsburgh [2]	2,401,245	151	124	12178	11626
San Francisco [2]	3,109,519	205	141	15083	15848

[1] Cutler and Young, eds., 1975
[2] all standard metropolitan statistical areas (SMSA)

TABLE 16, APPENDIX

DEATH CERTIFICATES: PATIENTS NOTED AS DEAD IN CLINICAL RECORDS

Patient	Sex	Final status	Underlying cause of death
1	F	died 1980	Renal cell carcinoma
2	F	died 1978	Hodgkin's disease
3	M	died 1978	Histiocytic lymphoma
4	M	died 1978	Cancer of the stomach
5	M	died 1976	Hodgkin's disease
6	F	died 1976	Hodgkin's disease, stomach
7	M	died 1975	Cancer of the stomach
8	M	died 1975	Hodgkin's disease
9	F	died 1972	Lymphosarcoma [1]
10	M	died 1971	Cancer of the right maxilla [1]
11	M	died 1970	Kaposi's syndrome, Hodgkin's [2]
12	F	died 1970	Acute pulmonary embolism [2]
13	M	died 1970	Lymphosarcomatosis [2]
14	M	died 1970	Cancer of the cervix [1]
15	M	died 1970	Cancer of the lung [1]
16	F	?died 1981	?Hodgkin's disease
17	F	?died 1970	?Hodgkin's disease
18	M	?died 1969	?Hodgkin's disease

[1] excluded from study
[2] included in study

TABLE 17, APPENDIX

DEATH CERTIFICATES: PATIENTS LOST TO FOLLOWUP

Patient	Sex	Month/year of Last record	Final status
1	M	1/1980	No death certificate [1]
2	M	3/1980	Moved to Ontario
3	F	11/1980	No death certificate [1]
4	M	5/1980	No death certificate [1]
5	F	3/1979	Moved to Labrador
6	F	1/1978	Moved to Quebec
7	M	1/1978	No death certificate [1]
8	M	1/1978	Moved to Ontario
9	M	4/1973	No death certificate [1]
10	M	9/1971	No death certificate [1]
11	F	3/1965	No death certificate [1]

[1] assumed alive

TABLE 18, APPENDIX

DEATH CERTIFICATES: REVIEW OF INFORMATION ON CERTIFICATES n = 46

Deaths in hospital = 87 percent (40)	Deaths at home = 13 percent (6)
1. Distribution by hospital 65 percent in General Hospital (26) 15 percent in cottage hospitals (6) 10 percent in Central Newfoundland Hospital (4) 7 percent in Western Memorial Hospital (3) 3 percent in hospitals outside the province (1)	1. Distribution by census division Division 1 (1) Division 2 (1) Division 4 (1) Division 6 (1) Division 8 (1) Division 9 (1)
2. Interval from death to registration range = 1 to 140 days mean = 13 days median = 7 days	2. Interval from death to registration range = 4 to 171 days mean = 68 days median = 7 days
3. Certificate signed by physician = 98 percent (39) 1 signed by priest	3. Certificate signed by physician = 83 percent (5) 1 signed by public health nurse

TABLE 19, APPENDIX

HOSPITAL ADMISSIONS: SUMMARY OF INFORMATION ON LISTING

Year	Variables on Listing x = present							Admissions Information					Quality of Data			
	Sex	Age	Hospital code	District code	Community code	MCP	Chart Number	Total admission	Total patients	Average admission per patient	Range of admission per patient	Admissions outside province	Number untraceable records	Number questionable records	Number chart numbers provided	Detectable errors in listing[1]
1965	X	X	X	X				24	14	1.7	1-4	0	2	2	3	1
1966	X	X	X	X				27	16	1.7	1-3	2	0	7	4	0
1967	X	X	X	X				24	17	1.4	1-3	0	1	0	8	0
1968	X	X	X	X				24	11	2.2	1-7	2	1	5	10	0
1969	X	X	X	X				24	19	1.3	1-3	3	0	3	5	0
1970	X	X	X	X		X		39	21	1.9	1-6	5	3	1	25	8
1971	X	X	X		X	X		50	21	2.4	1-10	4	2	0	25	8
1972	X	X	X		X	X		45	21	2.1	1-7	7	1	4	30	10
1973	X	X	X		X	X		50	27	1.9	1-8	7	0	0	32	6
1974	X	X	X		X	X	X	50	23	2.2	1-8	6	0	3	45	12
Totals								357				36	10	25		45

[1] Non-existant hospital codes, MCP digit errors, MCP missing, residence code error, residence code missing.

TABLE 20, APPENDIX

HOSPITAL ADMISSIONS: DISTRIBUTION OF ADMISSIONS n = 357

	n	percent
Seen at General Hospital, St. John's	48	57
Seen in St. John's, Hospitals General Hospital Grace General Hospital Janeway Children's Hospital St. Clare's Mercy Hospital	66	79
Seen in St. John's, Grand Falls, Corner Brook, or Carbonear	74	88
Seen in major hospitals, regional and cottage hospitals[1]	79	94
Seen in provincial hospitals and outside the province[2]	84	100

[1] 5 patients seen in regional and cottage hospitals only

[2] 5 patients seen in hospitals outside the province only

TABLE 21, APPENDIX

HOSPITAL ADMISSIONS: SEQUENCE OF PATIENT ADMISSIONS n = 81[1]

	1965-1969 (n = 34)		1970-1974 (n = 47)	
	n	percent	n	percent
Admitted year of diagnosis	32	94	37	79
Admitted year of death	17	50	16	34
Admitted 2nd year of illness	8	21	18	38
Admitted 3rd year of illness	10	26	4	8
Admitted 4th year of illness	9	23	3	6
Admitted 5th year of illness	5	13	1	2
Admitted 6th year of illness	4	12	NA	NA
Admitted 7th year of illness	1	3	NA	NA
One admission only	10	29	17	36

[1] Excluding three patients on whom not enough information was available.

TABLE 22A, APPENDIX

FINAL LIST OF PATIENTS: NEWLY DIAGNOSED CASES n=90

Date Dx[1]	Sex	Residence Dx[2]	Birthplace	Age at Dx	Marital Status
	M	05	-	-	-
3/65	M	06	06	6	S
4/65	M	08	-	13	S
5/65	M	09	09	20	S
7/65	M	01	85	14	S
9/65	M	07	07	16	S
1/66	M	09	09	12	S
2/66	M	02	02	68	S
5/66	M	01	01	27	M
7/66	M	05	09	31	M
8/66	M	01	01	12	S
8/66	M	04	01	58	M
2/67	M	01	01	30	M
4/67	F	05	99	54	M
4/67	M	04	04	55	M
5/67	F	01	07	18	S
5/67	F	01	-	19	M
5/67	M	01	84	36	M
8/67	F	01	01	48	M
10/67	F	06	-	18	S
11/67	F	01	01	37	M
11/67	M	05	-	71	M
1/68	F	05	99	42	M
5/68	F	06	01	16	S
8/68	M	01	-	11	S
10/68	M	09	09	8	S
10/68	F	02	-	21	S
1/69	M	01	-	71	M
2/69	M	04	04	43	M
3/69	M	01	-	19	S

[1] Dx=diagnosis
[2] Residence=census division

TABLE 22A, APPENDIX

FINAL LIST OF PATIENTS: NEWLY DIAGNOSED CASES n=90

Date Dx[1]	Sex	Residence Dx[2]	Birthplace	Age at Dx	Marital Status
4/69	M	01	01	21	S
4/69	M	06	-	59	M
4/69	M	01	-	26	M
8/69	F	01	01	34	M
10/69	F	01	01	19	M
12/69	F	02	01	67	M
12/69	F	02	-	70	M
1/70	F	08	08	57	M
1/70	M	08	-	68	M
5/70	F	01	01	14	S
5/70	M	01	-	28	S
7/70	M	05	01	52	M
10/70	M	08	-	49	M
10/70	M	09	09	60	M
10/70	M	03	03	18	S
10/70	M	04	-	18	S
11/70	M	01	01	55	S
11/70	M	01	01	53	M
12/70	M	10	08	18	S
1/71	F	01	-	13	S
2/71	M	05	-	26	M
2/71	F	01	07	41	M
4/71	M	01	-	22	S
6/71	M	06	-	48	M
7/71	M	01	-	46	M
8/71	M	03	-	34	M
8/71	M	05	-	20	S
8/71	M	06	-	61	M
9/71	M	01	-	39	M
12/71	M	10	10	24	S

1 Dx=diagnosis
2 Residence=census division

TABLE 22A, APPENDIX

FINAL LIST OF PATIENTS: NEWLY DIAGNOSED CASES n=90

Date Dx[1]	Sex	Residence[2] Dx	Birthplace	Age at Dx	Marital Status
/72	M	01	01	76	M
2/72	F	01	01	3	S
6/72	M	05	-	22	S
6/72	M	01	01	35	M
7/72	F	09	09	6	S
9/72	F	08	08	85	M
10/72	M	08	-	20	M
10/72	M	10	09	35	M
12/72	M	03	03	22	S
12/72	F	09	09	20	S
1/73	F	01	01	64	M
2/73	F	01	-	25	S
3/73	F	01	-	44	M
4/73	F	01	-	26	M
4/73	M	07	07	54	M
6/73	M	09	09	10	S
6/73	M	08	08	20	S
6/73	M	01	01	31	M
7/73	F	01	01	22	S
7/73	M	03	-	63	M
8/73	F	06	86	26	M
10/73	F	10	06	16	S
11/73	M	01	-	17	S
11/73	F	04	-	19	M
1/74	M	04	04	45	S
5/74	M	01	-	25	S
5/74	M	01	-	22	M
11/74	M	01	-	22	M
11/74	F	07	-	23	S
12/74	M	09	09	4	S

[1] Dx=diagnosis
[2] Residence=census division

TABLE 22B, APPENDIX (continued)

FINAL LIST OF PATIENTS: NEWLY DIAGNOSED CASES n=90

Patient	Stage Dx[1]	Type Dx	Date Death	Date LTF[2]	Occupation	Sibship Size	Certain/ Probable
1	IVB	-	9/79	-	Clerical	-	P
2	-	GR	2/69	-		-	C
3	-	PG	-	12/81	Student	7	P
4	B	GR	10/65	-	Not stated	14	C
5	IA	NS	-	3/81	Student	3	C
6	-	-	10/66	-	Student	-	C
7	A	GR	7/67	-	Student	4	C
8	IIA	-	5/66	-	Not stated	-	C
9	IIB	GR	12/68	-	Clerical	2	C
10	-	-	7/66	-	Medical	6	C
11	IIA	LP	10/81	-	Student	8	C
12	B	SA	4/67	-	Teacher	-	P
13	-	SA	3/69	-	Clerical	-	C
14	IIIB	PG	9/70	-	Housewife	-	C
15	B	GS	5/67	-	Transport	2	C
16	A	NS	-	11/81	Not stated	-	C
17	IIA	NS	-	6/81	Housewife	-	C
18	IIB	NS	8/67	-	Managerial	-	C
19	IA	GR	4/69	-	Housewife	-	C
20	A	NS	-	11/81	Not stated	-	C
21	IA	GR	9/81	-	Housewife	-	C
22	-	SA	12/67	-	Retired	-	C
23	-	-	3/65	-	Housewife	-	C
24	IIB	GR	9/70	-	Student	-	C
25	IIA	-	-	8/81	Student	-	C
26	A	-	12/70	-	Student	7	C
27	IIA	NS	11/74	-	Medical	-	C
28	A	PG	8/70	-	Laborer	-	C
29	B	GR	5/69	-	Laborer	-	C
30	IIIB	DF	-	9/73	Transport	-	C

1 Dx=diagnosis
2 LTF=lost to followup

TABLE 22B, APPENDIX (continued)

FINAL LIST OF PATIENTS: NEWLY DIAGNOSED CASES n=90

Patient	Stage Dx[1]	Type Dx	Date Death	Date LTF[2]	Occupation	Sibship Size	Certain/ Probable
31	IIA	NS	-	8/81	Clerical	-	C
32	IIA	LD	11/70	-	Trades	2	C
33	IIA	NS	-	5/80	Not stated	-	C
34	IIB	-	-	5/81	Clerical	4	C
35	IIB	MC	9/78	-	Student	5	C
36	IA	PG	11/74	-	Not stated	-	C
37	-	PG	-	8/81	Not stated	-	C
38	IVA	MC	2/72	-	Housewife	4	P
39	IVB	-	11/70	-	Transport	-	C
40	IIA	MC	-	11/81	Student	6	C
41	IVA	NS	-	10/81	Not stated	-	C
42	IIA	MC	3/72	-	Clerical	-	P
43	IA	MC	5/74	-	Trades	-	C
44	B	-	3/71	-	Forestry	11	P
45	IVB	GR	8/71	-	Trades	10	C
46	IA	MC	-	8/81	Not stated	-	C
47	IIIB	NS	1/73	-	Clerical	3	C
48	B	-	3/71	-	Clerical	-	C
49	IIA	NS	-	2/82	Transport	-	C
50	IIA	NS	-	1/78	Student	4	C
51	IIIA	NS	-	3/81	Teacher	-	C
52	IIA	MC	8/71	-	Housewife	-	C
53	IIIA	MC	-	10/81	Trades	-	C
54	IIB	MC	-	10/81	-	2	C
55	IIIB	MC	12/74	-	Managerial	-	C
56	IVB	MC	-	12/81	Processing	3	C
57	IA	MC	-	10/81	Trades	10	C
58	-	SA	-	9/71	Trades	-	P
59	IIA	MC	1/73	-	Medicine	-	C
60	IVB	SA	-	-	Forestry	-	C

[1] Dx=diagnosis
[2] LTF=lost to followup

TABLE 22B, APPENDIX (continued)

FINAL LIST OF PATIENTS: NEWLY DIAGNOSED CASES n=90

Patient	Stage Dx [1]	Type Dx	Date Death	Date LTF [2]	Occupation	Sibship Size	Certain/ Probable
61	-	-	9/75	-	Managerial	-	C
62	I	MC	-	8/81		12	C
63	IIIA	NS	-	8/81	Teacher	-	C
64	IA	MC	-	1/81	Forestry	-	C
65	IVB	LD	-	8/81	Student	3	C
66	IIA	MC	11/73	-	Housewife	-	C
67	IIB	NS	-	10/81	Trades	4	C
68	IA	LD	-	3/81	Forestry	13	P
69	IIIB	NS	6/73	-	Clerical	6	C
70	IA	NS	10/73	-	Medicine	11	C
71	IVB	-	3/76	-	Housewife	1	C
72	IA	LP	-	3/81	Teacher	-	C
73	IIA	NS	-	8/81	Housewife	-	C
74	IIA	NM	-	8/81	Teacher	-	P
75	IIIA	NS	4/75	-	Trades	8	C
76	IIA	MC	5/76	-	Student	9	C
77	IIIA	MC	-	1/78	Student	6	C
78	IIIB	NM	11/74	-	Trades	8	C
79	IIIB	-	-	9/81	Clerical	10	P
80	-	NS	9/74	-	Laborer	-	C
81	IIIA	MC	-	12/81	Housewife	2	C
82	IIB	MC	-	3/79	Student	5	C
83	IA	MC	-	9/81	Student	7	C
84	IA	NS	-	11/81	Student	10	C
85	-	LD	-	1/80	Unemployed	7	C
86	A	LP	-	8/81	Teacher	-	C
87	-	MC	3/80	-	Trades	6	C
88	IIA	NS	-	12/81	Trades	-	C
89	IIIB	MC	-	11/80	Housewife	-	C
90	IIIB	MC	-	11/81		13	C

[1] Dx=diagnosis
[2] LTF=lost to followup

TABLE 23, APPENDIX

FINAL LIST OF PATIENTS: PREVALENT PATIENTS n=15

Date Dx[1]	Sex	Residence	Age at Dx	Marital Status	Date Death	Date LTF[2]	Occupation
6/50	M	09	34	M	6/77	-	-
1/54	F	09	7	S	6/69	-	Student
6/56	M	08	3	S	-	1/81	-
4/57	M	07	26	M	7/66	-	Laborer
9/57	F	01	17	S	3/74	-	Not stated
12/59	M	01	15	S	3/75	-	-
7/60	F	01	32	M	2/65	-	Not stated
5/61	M	01	19	S	-	10/79	-
3/62	F	01	37	M	10/66	-	Housewife
5/62	M	01	32	M	8/70	-	Teacher
5/62	M	01	21	S	5/67	-	-
10/62	F	01	19	S	2/65	-	Not stated
10/62	F	02	32	M	10/65	-	Housewife
3/63	F	01	57	M	3/66	-	Housewife
9/64	M	01	39	M	11/65	-	-

[1] Dx=diagnosis
[2] LTF=lost to followup

TABLE 24, APPENDIX

FINAL LIST OF PATIENTS: DEATHS n=46

Date Death	Sex	Residence at Death	Birthplace	Age at Death	Marital Status
1965	M	09	09	20	S
1965	F	01	01	20	S
1965	M	06	08	48	M
1965	F	02	02	35	M
1965	F	01	01	36	M
1966	M	02	02	67	M
1966	F	01	01	40	M
1966	F	01	01	89	M
1966	M	05	09	31	M
1966	M	07	07	34	M
1966	M	07	07	16	S
1967	M	04	01	59	M
1967	M	04	04	56	M
1967	M	01	84	36	M
1967	M	01	01	25	S
1967	M	09	09	13	S
1967	M	05	-	71	M
1968	M	01	01	29	M
1969	M	04	04	43	M
1969	M	01	01	32	M
1969	F	09	09	23	S
1969	M	06	06	11	S
1969	F	01	01	49	M
1970	M	09	09	10	S
1970	M	06	-	60	M
1970	M	01	-	38	-
1970	M	01	-	71	M
1970	M	08	-	68	M
1970	F	05	99	58	M
1971	M	09	09	60	M

TABLE 24, APPENDIX (continued)

FINAL LIST OF PATIENTS: DEATHS n=46

Date Death	Sex	Residence at Death	Birthplace	Age at Death	Marital Status
1971	M	03	03	19	S
1971	F	01	07	42	M
1971	M	01	01	51	M
1972	M	05	01	52	M
1972	F	08	08	59	M
1973	M	03	03	22	S
1973	F	09	09	21	S
1973	M	01	-	40	M
1973	M	01	01	57	S
1973	F	08	08	85	M
1974	F	02	-	72	M
1974	M	08	-	52	M
1974	M	01	-	49	M
1974	M	01	01	32	M
1974	M	03	-	64	M
1974	F	02	-	27	S

TABLE 25, APPENDIX

INCIDENCE: AVERAGE ANNUAL ADJUSTED RATES, NEWFOUNDLAND AND CENSUS DIVISIONS, 1965-1974

Region	Sex	Observed Cases	Expected Cases	SIR	Adjusted rate
Canada	M			100	3.4
	F			100	2.2
Nfld	M	60	83	73	2.5
	F	30	50	60	1.3
Div.1	M	22	35	63	2.1
	F	15	22	68	1.5
Div.2	M	1	4	25	0.8
	F	3	3	100	2.6
Div.3	M	4	4	100	3.7
	F	-	2	-	-
Div.4	M	5	4	125	4.3
	F	1	2	50	0.9
Div.5	M	7	7	100	3.5
	F	2	4	50	1.0
Div.6	M	4	6	67	2.3
	F	3	4	75	1.8
Div.7	M	3	7	43	1.5
	F	1	4	25	0.6
Div.8	M	5	8	63	2.2
	F	2	5	40	1.0
Div.9	M	6	3	200	5.9
	F	2	2	100	2.2
Div.10	M	3	5	60	2.2
	F	1	2	50	1.0

TABLE 26, APPENDIX

INCIDENCE: ANNUAL CRUDE INCIDENCE RATES, CANADA AND PROVINCES, 1969-74

Year	Sex	Canada		Nfld		PEI		NS		NB		Que		Ont		Man		Sask		Alta		BC	
		n	rate	n	rate	n	rate	n	rate	n	rate	n	rate	n	rate	n	rate	n	rate	n	rate	n	rate
1969	M	238	3.4	6	2.3	1	1.8	9	2.3	9	2.8	99	3.3	NA		23	4.7	23	4.9	20	2.4	48	4.4
	F	150	2.2	4	1.6	1	1.8	7	1.8	1	0.3	75	2.5			10	2.0	7	1.5	14	1.7	28	2.6
1970	M	221	3.2	0	3.8	-	-	15	3.8	13	4.1	88	2.9	NA		16	3.2	13	2.8	29	3.5	36	3.3
	F	161	2.3	2	0.8	1	1.8	7	1.8	5	1.6	75	2.5			10	2.0	10	2.2	22	2.7	29	2.7
1971	M	223	3.2	9	3.4	-	-	8	2.0	9	2.8	82	2.7	NA		14	2.8	23	4.9	37	4.5	42	3.8
	F	149	2.2	2	0.8	-	-	9	2.3	3	1.0	55	1.8			17	3.4	6	1.3	21	2.6	35	3.2
1972	M	226	3.2	6	2.3	2	3.6	10	2.5	7	2.2	113	3.8	NA		15	3.0	19	4.0	24	2.9	31	2.8
	F	149	2.2	4	1.6	-	-	9	2.3	7	2.2	53	1.7			11	2.2	10	2.2	24	3.0	31	2.9
1973	M	251	3.6	6	2.3	1	1.8	20	5.0	17	5.3	111	3.7	NA		15	3.0	16	3.4	22	2.7	41	3.7
	F	155	2.2	8	3.1	-	-	7	1.8	6	1.9	62	2.0			9	1.8	13	2.9	19	2.4	30	2.8
1974	M	279	4.0	6	2.3	4	7.1	11	2.8	12	3.8	121	4.0	NA		21	4.2	16	3.4	33	4.0	55	5.0
	F	146	2.1	1	0.4	1	1.8	5	1.3	4	1.3	60	2.0			19	3.8	10	2.2	24	3.0	21	1.9
Total	M	1438	3.44	43	2.7	8	2.3	73	3.1	67	3.5	614	3.4	NA		4	3.5	110	3.9	165	3.3	253	3.9
	F	910	2.22	21	1.4	3	0.9	44	1.2	26	1.4	380	2.1			76	2.6	56	2.0	124	2.6	174	2.7

TABLE 27, APPENDIX

INCIDENCE: AVERAGE ANNUAL ADJUSTED RATES, CANADA AND PROVINCES, 1969-1974

Region	Sex	Observed Cases	Expected Cases	SIR	Adjusted rates
Canada	M			100	3.4
	F			100	2.2
NFLD	M	43	49.2	87	3.0
	F	21	30.0	70	1.5
PEI	M	8	12.0	67	2.3
	F	3	7.2	42	0.9
NS	M	73	82.2	89	3.0
	F	44	51.6	85	1.9
NB	M	67	64.8	103	3.5
	F	26	40.8	64	1.4
QUE	M	614	611.4	100	3.4
	F	380	397.8	96	2.1
MAN	M	104	105.6	98	3.3
	F	76	66.0	115	2.5
SASK	M	110	99.6	110	3.8
	F	56	59.4	94	2.1
ALTA	M	165	168.0	98	3.3
	F	124	100.8	123	2.7
BC	M	253	237.0	107	3.6
	F	174	146.4	119	2.6

TABLE 28, APPENDIX

INCIDENCE: AVERAGE ANNUAL AGE-SPECIFIC RATES, CANADA AND PROVINCES, 1969-74

Region		Age Groups																	
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	ALL AGES
Nfld	M	0.5	-	1.0	2.8	6.8	3.8	2.4	3.8	1.4	5.6	4.4	3.2	6.3	5.9	4.1	5.9	-	-	2.7
	F	0.6	0.5	1.0	1.7	2.2	2.9	1.3	-	2.9	-	-	1.8	2.4	3.0	3.7	-	8.7	-	1.4
PEI	M	-	-	2.6	2.9	-	-	5.7	5.8	-	6.2	6.4	12.5	-	-	-	-	-	-	2.3
	F	-	-	-	8.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.9
NS	M	0.5	0.4	0.8	1.2	4.8	5.0	2.3	2.4	4.2	4.9	4.2	5.3	6.3	7.1	7.9	8.0	8.8	-	3.1
	F	-	-	0.4	2.1	2.0	2.6	0.79	0.82	1.7	2.4	2.4	6.2	2.2	2.7	9.9	4.1	3.3	-	1.2
NB	M	-	-	0.9	2.8	4.0	4.8	8.9	1.1	3.2	3.1	4.5	6.0	5.7	11.3	15.4	6.9	11.7	8.9	3.5
	F	-	-	-	1.9	3.0	0.85	1.0	-	2.1	2.0	2.2	1.2	4.3	5.3	-	5.6	-	-	1.4
Que	M	0.1	0.4	0.5	2.5	6.9	5.2	4.5	3.4	4.5	4.5	4.0	4.9	4.5	6.8	7.8	7.5	4.9	5.3	3.4
	F	0.1	0.4	0.9	2.4	2.8	2.9	3.1	1.8	1.8	1.7	2.1	2.8	5.5	3.6	3.4	4.7	4.7	1.1	2.1
Man	M	-	0.3	0.6	2.7	3.9	9.7	1.8	5.0	3.1	1.8	4.7	3.5	6.7	6.3	9.0	12.0	15.2	4.6	3.5
	F	-	-	0.7	1.8	3.5	4.6	4.8	3.2	1.9	2.9	2.6	2.0	0.8	6.0	9.1	6.6	7.5	6.7	2.6
Sask	M	0.4	0.7	1.6	2.7	6.2	5.6	3.5	5.4	4.5	1.9	2.0	9.2	8.4	6.2	10.4	3.7	15.3	7.3	3.9
	F	-	0.3	1.3	1.4	2.5	2.5	2.1	3.5	1.3	2.6	1.3	0.72	3.6	10.1	2.9	5.4	-	10.6	2.0
Alta	M	-	0.2	0.4	2.4	5.0	7.0	4.3	4.5	2.7	4.5	4.0	5.1	5.7	8.4	8.9	9.6	2.3	10.4	3.3
	F	-	0.2	0.9	3.2	4.4	5.4	4.7	2.1	2.2	2.7	1.8	2.6	3.3	6.6	4.4	7.5	-	-	2.6
BC	M	0.4	0.6	1.0	3.4	5.2	6.5	6.4	2.2	2.7	2.6	3.0	5.7	7.1	8.8	5.7	11.8	20.5	5.8	3.9
	F	-	-	1.4	2.2	4.9	3.6	4.9	1.9	2.2	3.3	2.0	2.8	3.9	3.4	8.5	5.4	3.3	5.9	2.7
Canada	M	0.2	0.4	0.7	2.6	5.8	5.9	4.5	3.4	3.8	3.9	3.8	5.4	5.6	7.5	7.9	8.2	10.4	5.9	3.4
	F	0.1	0.3	0.9	2.3	3.3	3.3	3.3	1.9	1.9	2.2	2.0	2.7	4.1	4.5	5.0	5.1	3.5	3.4	2.2

TABLE 29, APPENDIX

CLINICAL STAGE AT DIAGNOSIS BY STAGE AND BY AGE GROUP

	n	percent of total	0-14	15-29	30-44	45-59	60+	Total
By stage								
IA	13	23.6	7.7	46.2	23.1	15.4	7.7	100.0
IB	-	-	-	-	-	-	-	
IIA	19	34.5	26.3	36.8	15.8	10.5	10.5	100.0
IIB	8	14.5	-	62.5	25.0	12.5	-	100.0
IIIA	6	10.9	-	83.3	-	16.7	-	100.0
IIIB	9	16.4	11.1	44.4	11.1	33.3	-	100.0
IVA	2	3.6	-	50.0	-	50.0	-	100.0
IVB	7	12.7	14.3	28.6	14.3	-	28.6	100.0
Total	64							
By age [1]			n=8	n=30	n=10	n=10	n=5	63
IA			12.5	20.0	30.0	20.0	20.0	
IB			-	-	-	-	-	
IIA			62.5	23.3	30.0	20.0	40.0	
IIB			-	16.7	20.0	10.0	-	
IIIA			-	16.7	-	10.0	-	
IIIB			12.5	13.3	10.0	30.0	-	
IVA			-	3.3	-	10.0	-	
IVB			12.5	6.7	10.0	-	40.0	
Total			100.0	100.0	100.0	100.0	100.0	
Not staged=26			19.2	19.2	15.4	15.4	30.8	

[1] No age stated for one male (14.3 percent of stage IVB)

TABLE 30, APPENDIX

HISTOPATHOLOGIC TYPE AT DIAGNOSIS BY TYPE AND BY AGE GROUP

	n	percent of total	age groups 0-14	15-29	30-44	45-59	60+	Total
By type								
PG [1]	5	26.3	20.0	-	-	20.0	60.0	100
GR	9	47.4	22.2	44.4	22.2	11.1	-	100
SA	5	26.3	-	20.0	20.0	20.0	40.0	100
Total	19							
By age			n=3	n=5	n=3	n=3	n=5	19
PG			33.0	-	-	33.1	60.0	
GR			67.0	80.0	67.0	33.1	-	
SA			-	20.0	33.0	33.1	40.0	
Total			100.0	100.0	100.0	100.0	100.0	
By type								
LP	3	5.4	33.3	66.6	-	-	-	100
NS	22	40.0	9.0	68.2	9.0	9.0	4.5	100
MC	26	47.0	15.4	38.5	19.2	19.2	7.7	100
LP	4	7.3	25.0	-	25.0	50.0	-	100
Total	55							
By age			n=8	n=27	n=8	n=9	n=3	55
LP			13.0	7.4	-	-	-	
NS			25.0	55.6	25.0	22.2	33.3	
MC			50.0	37.0	40.0	55.6	67.6	
LD			13.0	-	12.5	22.2	-	
Total			100.0	100.0	100.0	100.0	100.0	
Not classified=16			12.5	18.8	18.8	12.5	31.3	7.7 [2]

[1] PG=paragranuloma; GR=granuloma; SA=sarcoma
LP=lymphocyte predominant; NS=nodular sclerosis;
MC=mixed cellularity; LD=lymphocyte depletion

[2] no age stated for one male patient

TABLE 31, APPENDIX

PREVALENCE: NEWFOUNDLAND CENSUS DIVISIONS, 1965-1974

Division	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974
1	x	x	x	x	x	x	x	x	x	x
	x	x	x	x	x	x	x	x	x	x
	x	x	x	x	x	x	x	x	x	x
	x	x	x	x	x	x	x	x	x	D
	x	x	x	x	x	D				
	x	x	D							
	x	D								
	x	D								
	D									
	D									
	D									
		x	x	x	x	x	x	x	x	x
		x	x	D						
			x	x	x	x	x	x	x	x
			x	x	x	x	x	x	x	x
			x	x	x	x	x	x	x	x
			x	x	D					
			x	x	D					
			D							
				x	x	x	x	x	x	x
					x	x	x	x	x	x
					x	x	x	x	x	x
					x	x	x	x	x	x
					x	x	x	x	x	x
					x	x	x	x	LTF	
					x	D				
						x	x	x	x	x
						x	x	x	x	x
						x	x	x	D	
						x	D			
							x	x	x	x
							x	x	x	x
							x	x	x	D
							x	x	D	
							D			
								x	x	x
								x	x	x
								x	x	x
									x	x
									x	x
									x	x
									x	x
									x	x
									x	x
									x	D
										x
										x

D=death; LTF=lost to followup

TABLE 31, APPENDIX (continued)

PREVALENCE: NEWFOUNDLAND CENSUS DIVISIONS, 1965-1974

Division	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974
2	D									
		D								
				x	x	x	x	x	x	D
					x	x	x	x	x	x
					x	x	x	x	x	D
3						x	D			
							x	x	x	x
								x	D	
									x	x
4		x	D							
			D							
					D					
						x	x	x	x	x
									x	x
										x
5		D								
			x	x	x	D				
			D							
				x	x	x	x	x	x	x
						x	x	D		
							x	x	x	x
							x	x	x	x
								x	x	x
										x
6	x	x	x	x	D					
			x	x	x	x	x	x	x	x
				x	x	D				
					x	D				
							x	x	x	x
							LTF			
									x	x
7	x	D								
	x	D								
									x	x
										x
										x

D=death; LTF=lost to followup

TABLE 31, APPENDIX (continued)

PREVALENCE: NEWFOUNDLAND CENSUS DIVISIONS, 1965-1974

Division	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974
8	x	x	x	x	x	x	x	x	x	x
	x	x	x	x	x	x	x	x	x	x
						x	x	x	x	D
						x	x	D		
						D				
								x	x	x
								x	D	
									x	x
9	x	x	x	x	x	x	x	x	x	x
	x	x	x	x	D					
	D									
		x	D							
				x	x	D				
						x	D			
								x	x	x
								x	D	
									x	x
										x
10						x	x	x	x	x
							x	x	x	x
								x	x	x
									x	x

D=death; LTF=lost to followup

TABLE 32, APPENDIX

MORTALITY: AVERAGE ANNUAL ADJUSTED DEATH RATES, NEWFOUNDLAND CENSUS DIVISIONS, 1965-74

Region	Observed Cases	Expected Cases	SMR	Adjusted rate
Nfld	46	62.3	74	1.1
Div.1	17	26.9	63	0.9
Div.2	4	3.2	125	1.7
Div.3	3	2.8	107	1.6
Div.4	3	2.8	107	1.5
Div.5	4	5.0	80	1.1
Div.6	3	4.3	70	1.0
Div.7	2	5.5	36	0.5
Div.8	4	5.9	68	0.9
Div.9	6	2.5	240	3.3
Div.10	0	2.8	-	-

TABLE 33, APPENDIX

MORTALITY: AVERAGE ANNUAL ADJUSTED DEATH RATES, CANADA AND PROVINCES, 1965-1974

Region	Sex	Observed Cases	Expected Cases	SMR	Adjusted rate
Canada	M			100	1.7
	F			100	1.0
NFLD	M	32	40.0	80	1.4
	F	14	22.3	63	0.6
PEI	M	7	10.3	68	1.1
	F	6	6.2	97	1.0
NS	M	59	70.2	84	1.4
	F	46	42.6	108	1.1
NB	M	56	54.3	103	1.8
	F	31	32.7	95	1.0
QUE	M	529	499.2	106	1.8
	F	354	307.9	115	1.2
ONT	M	641	677.4	95	1.6
	F	387	421.4	92	0.9
MAN	M	87	91.1	95	1.7
	F	64	54.9	117	1.2
SASK	M	85	88.6	96	1.6
	F	45	49.9	90	0.9
ALTA	M	137	140.7	97	1.7
	F	73	78.2	93	0.9
BC	M	237	204.8	116	2.0
	F	109	116.6	93	0.9

TABLE 34, APPENDIX

MORTALITY: AVERAGE ANNUAL AGE-SPECIFIC DEATH RATES, CANADA AND PROVINCES, 1965-1974

Region		Age Groups																	
		-4	-9	-14	-19	-24	-29	-34	-39	-44	-49	-54	-59	-64	-69	-74	-79	-84	85+	All Ages
Nfld	M	-	-	.90	0.7	.91	1.1	2.9	1.5	1.6	1.7	2.6	2.9	3.8	3.6	4.9	-	-	-	1.4
	F	-	-	-	-	1.3	.58	-	1.7	1.7	.92	-	2.2	-	-	2.2	-	-	21.1	0.6
PEI	M	-	1.5	-	-	-	-	-	-	-	3.7	3.9	3.8	-	-	19.7	-	-	-	1.1
	F	-	-	-	1.8	2.2	3.6	-	8.0	-	-	-	-	-	-	-	-	11.1	-	1.0
NS	M	-	.46	.23	-	.87	2.2	.46	1.9	.51	1.5	3.5	3.7	4.4	4.3	3.5	9.7	5.3	-	1.4
	F	-	.24	.24	1.0	.89	.78	-	-	1.5	.48	2.5	2.7	3.3	3.2	4.0	6.2	1.2	2.5	1.1
NB	M	.34	-	.26	-	1.4	1.9	1.8	2.5	1.9	2.5	1.3	2.9	3.4	6.8	10.8	14.5	3.5	5.4	1.8
	F	-	.29	-	-	.36	1.0	.61	1.9	-	3.0	2.0	-	1.7	4.2	3.9	1.7	7.9	7.2	1.0
Que	M	-	.12	.29	.67	1.9	2.1	2.3	2.0	3.3	3.1	3.1	2.9	3.0	4.9	6.1	5.5	5.3	2.1	1.8
	F	-	.10	.06	.59	1.2	1.3	1.3	.94	1.5	1.2	1.6	1.9	3.7	4.0	3.9	4.5	2.0	2.7	1.2
Ont	M	.03	.02	.25	.61	1.4	1.8	1.8	1.7	2.2	2.0	1.9	3.5	3.2	6.2	5.9	4.8	8.5	8.1	1.6
	F	-	.03	.05	.20	1.1	.78	.80	1.1	1.2	1.2	1.1	1.9	2.3	3.0	3.7	4.2	3.9	2.5	0.9
Man	M	-	.20	.19	.41	1.2	3.8	1.8	3.4	1.9	1.5	3.5	2.1	1.5	4.4	5.4	7.2	11.0	-	1.7
	F	-	-	-	.63	.71	1.8	.37	1.2	2.6	2.4	1.2	2.0	1.5	3.6	7.0	3.0	6.0	2.0	1.2
Sask	M	-	-	.19	.82	2.6	1.5	1.3	2.0	1.5	1.5	2.8	5.5	6.1	6.2	1.8	2.2	6.1	2.2	1.6
	F	-	-	-	.64	1.8	1.2	1.3	1.3	1.2	-	1.2	.87	2.1	2.0	2.6	1.1	4.5	10.6	0.9
Alta	M	-	.43	-	.85	1.7	1.3	1.8	2.3	2.0	2.9	1.3	4.0	6.4	1.8	6.0	8.6	4.1	4.2	1.7
	F	-	.11	.11	.63	.42	.85	1.0	.85	.66	1.6	.54	3.7	.79	3.0	4.6	5.4	5.4	-	0.9
BC	M	-	.28	-	.68	1.2	2.4	2.2	3.0	2.8	2.7	2.7	4.4	4.1	6.1	7.2	9.5	7.4	8.1	2.0
	F	-	.10	-	.31	.76	1.0	.62	.83	1.3	1.8	1.7	.74	2.6	2.6	4.4	2.8	2.6	4.5	0.9
Canada	M	.02	.15	.23	.62	1.5	2.0	1.9	2.1	2.4	2.4	2.5	3.5	3.6	5.3	6.0	7.2	6.8	6.4	1.7
	F	-	.10	.10	.43	1.0	1.0	.92	1.0	1.3	1.3	1.4	1.8	2.5	3.2	3.9	3.9	3.6	4.9	1.0

TABLE 35, APPENDIX

SURVIVAL: PERCENTAGE SURVIVAL AT 1, 3, 5, AND 10 YEARS n=90

	n	years 1	3	5	10
Histological type					
PG [1]	5	100	60	40	40
GR	9	67	22	11	-
SA	6	42	-	-	-
LP	3	100	100	100	-
NS	22	82	73	73	68
MC	26	81	65	62	51
LD	4	100	75	75	-
not classified	15	60	40	40	24
Stage					
IA	14	93	86	71	43
IIA	19	79	63	63	43
IIB	8	88	63	63	43
IIIA	6	83	67	67	67
IIIB	9	78	44	44	44
IVA	2	100	50	50	50
IVB	7	71	54	54	36
not staged	25	59	38	34	25
Total group	90	77	55	53	38

[1] PG=paragranuloma; GR=granuloma; SA=sarcoma
LP=lymphocyte predominant; NS=nodular sclerosis;
MC=mixed cellularity; LD=lymphocyte depletion

TABLE 36, APPENDIX

RISK FACTORS: DISTRIBUTION OF PATIENT BIRTHS n = 48

Census Division	Observed [1]	Expected [2]
1	21	19.6
2	1	2.8
3	2	2.4
4	3	2.4
5	0	3.6
6	2	3.4
7	4	3.2
8	4	4.4
9	10	2.2
10	1	4.1

[1] 5 patients born outside Newfoundland; birth certificates not found for 37 patients

[2] expected proportions calculated from averaged births, Newfoundland, 1974-1980

TABLE 37, APPENDIX

INTERNATIONAL COMPARISONS: AVERAGE ANNUAL ADJUSTED RATES

Region	Crude rates M	Crude rates F	Adjusted rates [1] M	Adjusted rates [1] F
A. This series				
1965-1974	2.3	1.2	2.5	1.3
1969-1974	2.6	1.2	3.0	1.5
B. Canada 1969-1974	3.4	2.2	3.4	2.1
C. TNCS				
white	3.9	2.8	3.8	2.5
black	2.8	1.1	3.0	1.2
D. CIFC				
Ibadan	2.0	0.9	3.8	2.0
Recife	2.3	1.7	2.5	2.0
Cali	2.8	1.3	3.5	1.8
Connecticut	4.1	3.4	4.0	3.1
New Mexico	3.9	2.7	3.9	2.4
Bombay	0.8	0.4	1.0	0.6
Israel	2.6	2.5	2.7	2.5
Miyagi	0.7	0.4	0.8	0.4
Okayama	1.8	1.1	1.6	0.9
Germany (GDR)	3.4	2.3	3.0	1.8
Iceland	4.0	1.6	4.0	1.5
Norway				
urban	3.2	2.5	2.7	2.1
rural	3.2	1.9	2.9	1.6
Birmingham	2.9	1.9	2.7	1.7
SW England	3.3	1.8	3.0	1.4
Hawaii				
Caucasian	3.2	2.1	3.7	2.2
Japanese	1.8	1.3	1.5	1.1
New Zealand				
Maori	2.0	1.1	3.1	1.1
non-Maori	2.9	1.7	2.8	1.5

[1] using world population, Waterhouse et al., 1976

TABLE 38, APPENDIX

RISK FACTORS: STEPWISE REGRESSION ANALYSIS OF INCIDENCE AND SOCIOECONOMIC VARIABLES

A. Male incidence by Newfoundland census division

average persons/household		
average persons/room	r^2	= 0.89371
	sd	= 0.55500
	p of F	= 0.0004

B. Female incidence by Newfoundland census division

no significant predictors

C. Male incidence by Canadian province (excluding Ontario)

no clothes dryer	r^2	= 0.47094
	sd	= 0.35586
	p of F	= 0.0412

D. Female incidence by Canadian province (excluding Ontario)

house value less than $7500	r^2	= 0.71258
	sd	= 0.33840
	p of F	= 0.0042

TABLE 39, APPENDIX

RISK FACTORS: CORRELATIONS BETWEEN SOCIOECONOMIC PREDICTOR VARIABLES AND INCIDENCE RATES

	Male Incidence NFLD	Female Incidence NFLD	Male Incidence CANADA[1]	Female Incidence CANADA
average persons/household	0.810	0.045	-0.589	-0.667
2+ families/household	0.071	-0.278	-0.603	-0.592
average children/family	0.701	0.143	-0.528	-0.614
average family income	0.233	-0.035	0.021	-0.105
family income < $3000	0.262	-0.136	-0.320	-0.519
% family heads with < grade 8	0.210	-0.054	-0.255	-0.717
% family heads not in labor force	0.186	0.028	-0.392	-0.606
% house value < $7500	0.117	-0.076	-0.516	-0.844
average persons/room	0.407	-0.033	-0.299	-0.324
% cold water only	0.221	-0.115	-0.373	-0.449
% no flush toilet	0.204	-0.168	-0.480	-0.558
% space heater only	0.237	0.015	-0.641	-0.786
% no fridge	0.524	0.136	-0.428	-0.330
% no freezer	-0.508	0.082	-0.479	-0.530
% no clothes dryer	0.116	0.046	-0.686	-0.749

[1] excluding Ontario